

Diovan® (Valsartan) Congestive Heart Failure

Advisory Committee Briefing Document

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List of abbreviations

ACE	Angiotensin I converting enzyme
ACEI	Angiotensin I converting enzyme inhibitor
AE	Adverse event
Ang II	angiotensin II
ALT	alanine aminotransferase (SGPT)
ANCOVA	analysis of covariance
Ang II	Angiotensin II
AST	Aspartate aminotransferase (SGOT)
AT _I	Angiotensin I receptor
AUC	Area under curve
AVPD	atrioventricular plane displacement
BB	beta blocker
BID	Twice a day
BL	Baseline
BP	Blood pressure
BUN	Blood urea nitrogen
CHD	Coronary heart disease
CHF	Congestive heart failure
Chg	Change
CI	confidence interval
CK, CPK	Creatine phosphokinase
cm	Centimeter
C _{max}	highest observed concentration
CO	cardiac output
CRF	Case Report/Record Form
CV	Cardiovascular
db	double-blind
dL	Deciliter
DSMB	Data safety monitoring board
enal	Enalapril
ETT	Exercise tolerance test
EUROQOL	European Quality of Life Questionnaire
FEV ₁	forced expiratory volume in one second
FVC	forced vital capacity
HF	Heart failure

ICRO	International Clinical Research Operations
IEC	Independent Ethics Committee
IMN	International Medical Nomenclature
IRB	Institutional Review Board
ISE	Integrated Summary of Efficacy
ISS	Integrated Summary of Safety
ITD	International Therapy Dictionary
ITT	intent-to-treat
iv	intravenous(ly)
kg	Kilogram
L	liter (1000 cc)
LDH	Lactic dehydrogenase
LHFQ	Living with Heart Failure Questionnaire
lis	Lisinopril
LS Mn Chg	least squares mean change
LSM	least squares mean
LVEF	Left ventricular ejection fraction
LVIDD	left ventricular end-diastolic internal diameter in diastole
m	Meters
mc	Multicenter
MEDDRA	Medical Dictionary for Regulatory Activities
mL	Milliliters
mm Hg	Millimeters of mercury
MUGA	multiple gated acquisition radionuclide angiography
NEC	Not elsewhere classified
ng	Nanogram
NOS	Not otherwise specified
NYHA	New York Heart Association
OD	omni die/once a day
p.o.	per os/by mouth/orally
PCWP	Pulmonary Capillary Wedge Pressure
pg	Picogram
PK	Pharmacokinetic
Plc	Placebo
PRA	plasma renin activity
pts	Patients

rand	Randomized
RAS	renin angiotensin system
SAE	Serious adverse event
SAP	Safety analyzable population
SD	standard deviation
SE	standard error
SGOT	serum glutamate-oxaloacetate-transaminase (AST)
SGPT	serum glutamate-pyruvate-transaminase (ALT)
SHR	spontaneously hypertensive rats
SOP	Standard Operating Procedures
TID	Three times a day
t _{max}	Time of occurrence for maximum drug concentration
val	Valsartan
Val-HeFT	Valsartan Heart Failure Trial
WBC	White blood cells
WHO	World Health Organization
WHODRL	World Health Organization Drug Reference List

1. Introduction and Rationale

This document summarizes the clinical data presented in a Supplemental New Drug Application for Diovan® (valsartan) that provides for a new indication, the treatment of patients with heart failure.

Heart failure is a progressive clinical syndrome resulting from impaired left ventricular performance. The most common causes of ventricular dysfunction are coronary artery disease and hypertension; many patients have no known cause, i.e. idiopathic cardiomyopathy. Impaired ventricular function results in the activation of compensatory mechanisms, primarily the adrenergic and renin angiotensin systems, that contribute to the patient's symptoms and lead to the progressive process of ventricular remodeling. The hallmark symptoms are impaired functional capacity, manifested by exercise intolerance, fatigue, dyspnea and symptoms of fluid overload. Treatment of heart failure is directed at improving symptoms, quality of life, and clinical outcomes. Current therapies include diuretics, the inotrope digoxin, the vasodilator combination hydralazine/nitrate, angiotensin converting enzyme (ACE) inhibitors, and beta blockers. Hydralazine/nitrate, ACE inhibitors and beta blockers have been shown to improve clinical outcomes in patients with heart failure. Mortality in heart failure is still unacceptably high, estimated at 50% in 5 years. Heart failure is a frequent cause of hospitalizations and, therefore, health care costs, particularly in the elderly. Both mortality and the incidence of hospitalizations for heart failure are increasing.¹ Therefore, new treatments that improve outcomes in heart failure are needed.

Activation of the renin angiotensin system (RAS) is one of the key factors in the development of symptoms and progression of heart failure. Increased activity of the RAS is considered to be responsible for vasoconstriction, sodium retention with volume expansion, norepinephrine release, and cardiac hypertrophy. Inhibitors of ACE interrupt the production of angiotensin II. These agents have been shown to have beneficial effects on symptoms and on morbidity and mortality in patients with heart failure and prevent the development of overt heart failure in patients with asymptomatic impaired left ventricular dysfunction. Guidelines for the treatment of heart failure recommend the use of ACE inhibitors in patients with symptomatic and asymptomatic left ventricular dysfunction, unless they cannot be tolerated.^{2,3,4,5,6}

There are, however, non-ACE enzymatic pathways for the formation of angiotensin II that are not blocked by ACE inhibitors, notably the enzyme, cardiac chymase.^{7,8} These alternative pathways may be especially important in the tissue formation of angiotensin II, so that inhibition of the RAS by ACE inhibitors is incomplete. In a study on left ventricular function in patients with heart failure taking ACE inhibitors, patients who ultimately deteriorated were found to have higher levels of angiotensin II than patients who remained stable.⁹

The efficacy of ACE inhibitors may also be limited by the fact that they are competitive inhibitors. Thus, high levels of angiotensin I resulting from ACE inhibition might drive continued production of angiotensin II; or suppression of angiotensin II might upregulate the angiotensin II receptor, thus increasing the sensitivity to angiotensin II. Furthermore, ACE, also known as kininase II, is not a very specific enzyme and has other possible substrates besides angiotensin I, such as bradykinin. Increased bradykinin levels which are thought to be

associated with the use of ACE inhibitors, may have important physiologic effects that are potentially beneficial or detrimental as in the case of ACE inhibitor-induced dry cough.¹⁰

Taken together, the proven beneficial effects of ACE inhibitors in cardiovascular diseases can be attributed to at least partial suppression of the formation of angiotensin II. The contribution of increased bradykinin levels to the beneficial effects seen with ACE inhibitors remains controversial at present.

Angiotensin receptor blockers interact with the renin angiotensin system at the level of the AT₁ receptor, which appears to mediate all of the known biological effects of angiotensin II, and the deleterious effects of angiotensin II in heart failure. Therefore, the actions of angiotensin II, whether produced by ACE or non-ACE mediated pathways, are prevented by AT₁ receptor blockade. Compensatory increases in plasma renin and angiotensin II result, thereby stimulating the unblocked AT₂ receptor, which may have beneficial effects on vascular and cardiac remodeling.¹¹ Therefore, these agents are expected to be beneficial in the treatment of heart failure.

The combination of angiotensin receptor blockers and ACE inhibitors may be synergistic in the treatment of heart failure by retaining the ACE inhibitor effects on bradykinin potentiation and by providing more complete inhibition of the renin angiotensin system through blockade of the AT₁ receptor.

Valsartan is an orally active, potent and specific competitive angiotensin II antagonist at the level of the AT₁ receptor subtype. Valsartan capsules were first developed for the treatment of hypertension and have been approved by FDA for this use alone or in combination with other antihypertensive agents since 1996. A tablet formulation was approved July 18, 2001. The objective of the current development program is to seek marketing authorization for the use of valsartan in the treatment of heart failure.

Valsartan has also shown beneficial effects in patients with heart failure (HF). Clinical trial data enclosed has demonstrated the safety and efficacy of valsartan in patients with HF. The data presented in this Briefing Summary shows that:

Valsartan 40-160 mg BID in combination with existing therapies for HF is efficacious in the treatment of patients with NYHA Class II-IV heart failure. This was demonstrated by improvements in outcomes, symptoms, including quality of life, and various surrogate endpoints as outlined below:

- Valsartan significantly reduced the risk by 13.2% ($p=0.009$) for the primary endpoint of time to first morbid event, defined as all-cause mortality, heart failure hospitalization, sudden death with resuscitation, and need for intravenous vasodilator or inotropic therapy compared to placebo (Protocol 107).
- Valsartan significantly reduced the risk by 27.5% ($p=0.00001$) for the secondary endpoint of time to first heart failure hospitalization compared to placebo (Protocol 107).
- The significantly favorable effect of valsartan on morbidity was generally consistent across all patient subgroups, including age, gender, race, region, HF etiology, baseline

NYHA Class, baseline ejection fraction, and baseline neurohormone levels. Some of these subgroups contained small sample sizes; and therefore, results should be interpreted cautiously. The significantly favorable effect was more pronounced in patients not being treated with other neurohormonal inhibitors (i.e. ACEI and beta blockers). A significantly favorable effect in favor of valsartan was also obtained in patients receiving either a beta blocker alone or ACE inhibitor alone. The addition of valsartan, however, to patients receiving both an ACE inhibitor and a beta-blocker did not appear to confer any additional benefits (Protocol 107).

- Valsartan demonstrated favorable effects on cardiac hemodynamics, including pulmonary capillary wedge pressure and/or pulmonary artery diastolic pressure (Protocols 103 and 104) and cardiac output and systemic vascular resistance (Protocol 103) compared to placebo.
- Valsartan demonstrated statistically significant favorable effects on ejection fraction (Protocols 106 and 107) and left ventricular volume compared to placebo (Protocol 107).
- Valsartan demonstrated statistically significant beneficial effects on NYHA Class, signs and symptoms, and quality of life compared to placebo (Protocol 107).
- Valsartan demonstrated statistically significant beneficial effects on aldosterone (Protocol 104) and norepinephrine and brain natriuretic peptide compared to placebo (Protocol 107).
- Valsartan demonstrated greater mean increases in exercise time from baseline compared to placebo, although statistical significance was not achieved, with the greatest improvements observed in patients not taking ACE inhibitors (Protocol 106).
- Valsartan was shown to be at least as effective as enalapril with respect to exercise capacity in patients previously stabilized on ACE inhibitors and directly switched to valsartan or enalapril (Protocol 110).

Safety findings were as follows:

- Valsartan is both safe and well-tolerated in this population
- In the double-blind controlled short-term trials (ie the primary dataset), for events whether or not study drug related, the differences between valsartan and placebo in the overall incidence of AEs (valsartan 72.5%; placebo 68.5%), SAEs (valsartan 16.7%; placebo 17.9%), and deaths excluding Study 107 (valsartan 1.3%; placebo 1.6%) were small.
- In long-term Study 107, for events whether or not study drug related, the differences between valsartan and placebo in the overall incidence of AEs (valsartan 91.6%; placebo 89.6%), SAEs (valsartan 51.2%; placebo 53.8%) and deaths (valsartan 20.1%; placebo 20.0%) were small.
- In both the primary dataset, and in long-term Study 107, the most frequently reported AEs whether or not study drug related were dizziness excluding vertigo (primary dataset: valsartan 17.3%; placebo 9.3%; long-term Study 107: valsartan 25.0%; placebo 18.1%), hypotension NOS (primary dataset: valsartan 6.6%; placebo 2.4%; long-term Study 107:

valsartan 13.8%; placebo 8.1%). These differences were statistically significant and not unexpected in this HF population. The majority of events were mild or moderate in severity.

- In the primary dataset, the most frequently reported AEs suspected to be related to study medication were dizziness excluding vertigo (valsartan 13.1%; placebo 5.8%), hypotension NOS (valsartan 5.5%; placebo 1.8%) and dizziness postural (valsartan 2.2%; placebo 0.9%). These differences were statistically significant and not unexpected in this HF population. The majority of events suspected to be related to study medication were mild or moderate in severity.
- In the primary dataset excluding Study 107, the most frequently reported causes of death were congestive cardiac failure (valsartan 0.5%; placebo 0%) and sudden death unexplained (valsartan 0.3%; placebo 0.8%).
- In long-term Study 107, the most frequently reported cause of death was sudden death unexplained (valsartan 7.7%; placebo 7.1%).
- Safety results for the double-blind placebo-controlled short-term trials were very similar to those for the primary dataset.
- The incidence of angioedema for valsartan-treated patients was low (5 valsartan patients vs 1 placebo patient), and none of the cases were considered serious. One case was suspected to be related to study medication and led to premature discontinuation. All 6 subjects were taking concomitant ACE inhibitors.
- The incidence of cough was comparable for valsartan and placebo (4.8% vs 4.9%) in the primary dataset.
- The vital signs data do not suggest a higher incidence of postural hypotension with valsartan compared to placebo; however, postural hypotension reported as adverse events was slightly higher for valsartan compared to placebo (2.1% for valsartan and 0.7% for placebo) in the primary dataset and in long-term Study 107 (3.8% for valsartan and 1.9% for placebo). Albeit small, these differences were statistically significant and not unexpected in this HF population. Most cases of postural hypotension were mild or moderate in severity.
- In long-term Study 107, the incidence of congestive cardiac failure aggravated (valsartan 11.0%; placebo 15.5%) and atrial fibrillation (valsartan 5.3%; placebo 7.9%) was lower in valsartan-treated patients than in placebo-treated patients.
- The incidence of adverse events was unrelated to the age, race or sex of the patients or use of ACE inhibitors or beta blockers at baseline.
- In the analysis of long-term exposure, the nature of the adverse experiences observed with valsartan were similar to those observed during trials of shorter duration. As expected, the incidence of adverse experiences increased as the duration of exposure increased in both the valsartan and placebo groups.

- The incidence of premature discontinuation due to AEs [(primary dataset excluding Study 107: valsartan 8.6%; placebo 3.7%) (long-term Study 107: valsartan 9.9%; placebo 7.3%)] was slightly higher for valsartan than for placebo with the primary reasons being dizziness excluding vertigo and hypotension NOS.
- Valsartan was associated with increases from baseline in serum creatinine, potassium (known side effects of valsartan), BUN, and uric acid more frequently than placebo-treated patients.
- Valsartan was associated with decreases in hemoglobin and hematocrit more frequently than placebo-treated patients. This is a known side effect of valsartan, and is consistent with previous experience with angiotensin receptor blockers and ACE inhibitors.
- Valsartan was not associated with neutropenia in this HF population.
- No special monitoring of laboratory parameters is necessary per se with valsartan, but the evaluation and monitoring of patients with HF, especially those receiving concomitant therapy with diuretics and other inhibitors of the RAS, should always include assessment of renal function.

1.1. Overview of clinical pharmacology studies

Pharmacokinetics of valsartan in heart failure (HF) patients are characterized in two separate pharmacokinetic studies (Protocols 102 and 105). Protocol 102 was a single dose, dose escalation, placebo controlled parallel group study to assess safety, tolerability, pharmacokinetic and hemodynamic measures of valsartan in Heart Failure (HF) patients. Protocol 105 was primarily a multiple dose study to evaluate the steady state pharmacokinetics and dose proportionality of valsartan in HF patients. The multiple dose study was conducted as requested by the FDA during an end of Phase II meeting on April 29, 1996. Summaries of study designs, results and conclusions from these two studies are presented in this Briefing Summary.

1.2. Overview of clinical studies

A total of 5 adequate and well-controlled trials have been presented in support of the claim that valsartan is efficacious in the treatment of HF. These 5 studies include 3 placebo-controlled studies (Studies 104, 106, and 107), 1 placebo- and active-controlled (lisinopril) trial (Study 103), and 1 active-controlled (enalapril) trial (Study 110). Study 107 was a long-term morbidity and mortality trial. In these five trials, one or more of the following endpoints were evaluated: morbidity and mortality, exercise capacity, hemodynamics, HF signs and symptoms, NYHA Class, quality of life, left ventricular function, left ventricular volume, and plasma neurohormone levels. These were all multi-center, double-blind, multiple dose, randomized, parallel group studies in adult patients (ie 18-80 years of age in Studies 103 and 104; ≥ 18 years of age in Studies 106, 107 and 110) with chronic stable HF (NYHA Class II-IV except Study 110 which included Class II-III patients). Patients in these studies were treated both with and without background ACE inhibitor and beta blocker therapy.

Regulatory guidelines and discussions with FDA

In order to register valsartan in heart failure, several regulatory requirements had to be satisfied. Investigational New Drug Application 40,783 for valsartan for the treatment of HF was filed October 6, 1992. The HF program was designed according to the December 7, 1987 (ie first draft) version of the FDA guideline "Proposed Guidelines for the Clinical Evaluation of Drugs for the Treatment of Heart Failure". The second draft of this guideline is dated October 22, 1998. At the time of the second draft of this guideline (also the subject of an FDA advisory committee meeting), two key trials were already underway: Study 106, and Study 107 (Val-HeFT).

An End of Phase II meeting with FDA to evaluate the Phase III plan and discuss labeling objectives took place on April 29, 1996. A follow-up teleconference was held on May 10, 1996. Ciba/Novartis and FDA agreed to the following:

- For Study 106, it was agreed that the Minnesota Living with Heart Failure Questionnaire could serve as a co-primary variable, as a benefit on exercise tolerance was not expected to be shown.
- No additional pivotal exercise tolerance testing studies beyond those already planned (ie Studies 106 and 107/sub-study 02) would need to be conducted.
- For Study 107, two primary efficacy endpoints (both all-cause mortality and a combined endpoint of morbidity and mortality) would be acceptable. In this case, the alpha level would be recalculated. It was agreed that the stopping rule would be based on mortality alone.
- For interim analysis and statistical penalties for Study 107, it was deemed acceptable to define trial termination based on a pre-specified total number of events to be reached. However, if at the end of 4 years, the pre-specified number had not been reached, and Ciba/Novartis wished to use the data to decide whether to continue the trial, a statistical penalty on the significance level to be used for the final analysis could be incurred. No statistical penalty would be incurred if the termination of the trial was based on a fixed number of events OR a fixed duration.
- A BID dosing regimen for Studies 106 and 107 was chosen (the once-a-day arms were dropped).
- The number of events that would determine the timing of interim analysis of Study 107 would be specified as either 700 or 800. (Protocol amendment 3, dated February 23, 1998, specified that interim analyses would be performed approximately every 6 months, beginning around March of 1998, allowing modifications to this schedule when warranted based upon the progress of the trial or the scheduling of DSMB meetings held to review interim results.)
- Pharmacokinetic data from HF patients given BID dosing would be provided.

2. Clinical pharmacology studies

The pharmacokinetics, pharmacodynamics and biopharmaceutics of valsartan have been well characterized; this data was provided in the original NDA for hypertension. Overall conclusions are provided below as a ready reference.

- Following oral administration, valsartan was rapidly absorbed (t_{\max} : ~2-4 hours). The bioavailability of valsartan capsules was approximately 60% relative to a phosphate buffered solution (pH: 6.8). Valsartan exhibited a biphasic disposition with elimination half-life of about 6 hours.
- The final market image (FMI) capsule is bioequivalent to the clinical capsule formulations used in the Phase III clinical safety/efficacy trials. The FMI film coated tablet has been shown to be bioequivalent to the FMI capsule.
- Food decreases the availability of valsartan by approximately 50%.
- The accumulation of valsartan following multiple dosing was minimal.
- Valsartan showed dose proportional increase in the extent of availability with an increase in dose in the range of 80-320 mg.
- The total plasma clearance was about 2.2 L/h and the volume of distribution was about 17 L. Valsartan is highly bound to plasma proteins (~97%).
- Fecal excretion is the primary route of elimination (>80%). The majority of elimination appears to be through the biliary route. Renal elimination accounted for about 10% of the dose. Valsartan undergoes little metabolism and a majority of it (~85%) is eliminated as unchanged drug in urine and feces.
- Although the pharmacokinetics of valsartan were more variable in elderly than in young subjects (>65 years), a dosage adjustment in the elderly subjects does not seem necessary.
- In general, valsartan dosage adjustments are not necessary in renal or hepatically impaired patients. However, care should be taken while dosing severely impaired patients.
- There were no clinically significant pharmacokinetic drug interactions between valsartan and several cardiovascular drugs (amlodipine, atenolol, digoxin, and warfarin), diuretics (hydrochlorothiazide and furosemide), H-2 blocker (cimetidine), NSAID (indomethacin), and anti diabetic agent (glyburide).
- Valsartan blocks AT1 receptors for at least 24 hours post dose as demonstrated by the angiotensin II challenge studies. Plasma angiotensin II and plasma renin activity increased following valsartan dosing.
- In hypertensive patients, mean blood pressure decreases were greater following valsartan than placebo. The pharmacodynamic effect of valsartan appeared to be lagging behind plasma concentration of valsartan.

2.1. Pharmacodynamics in HF patients

Pharmacodynamic effects of valsartan in HF patients were explored in a pilot single dose safety and tolerability study (Protocol 102). This was a multi-center, open-label, single-dose, randomized, placebo-controlled, parallel group trial of 2-3 weeks duration in patients with stable, chronic congestive heart failure. Single doses of valsartan 10, 20, 30, 40, 80 or 160 mg were administered orally under fasting conditions. Blood samples for pharmacokinetic, pharmacodynamic and hemodynamic measurements were obtained at 1, 2, 3, 4, 6, 8, 12, and 24 hours post-dose. An additional 5 h measurement was obtained for pulmonary capillary wedge pressure (PCWP) and cardiac output (CO). There were 3-5 patients for each dose group. Only descriptive statistics were generated for the PK and PD parameters.

All patients tolerated doses up to 160 mg.

There was no apparent trend between observed PRA, Ang II, aldosterone, PCWP, CO and plasma valsartan concentration. The only noticeable trend was between PRA and Ang II which is expected from a biochemical viewpoint. There was a slight tendency towards an increase in placebo adjusted mean change from baseline for PRA and Ang II concentration with an increase in plasma valsartan concentration. There was also a slight trend for a decrease in placebo adjusted mean change from baseline for aldosterone concentration and PCWP with an increase in plasma valsartan concentration. There was no apparent association between neurohormonal variables (PRA, plasma Ang II and aldosterone concentration) and hemodynamic variables (PCWP and CO), based on the placebo adjusted mean change from baseline data. These results should be interpreted carefully as the results were obtained following a single dose administration.

2.2. Pharmacokinetics in HF patients

A summary of the two pharmacokinetics studies is provided in Table 2-1.

Table 2-1. Summary of pharmacokinetic studies

Study No.	Topic	No. of Patients	Population
102	Hemodynamics/ Pharmacokinetics	Valsartan: 21 Placebo: 4	HF patients, NYHA Class III - IV Ejection fraction \leq 35%
105	Pharmacokinetics	Valsartan: 20 (18 completed)	HF patients, NYHA Class II - III Ejection fraction \leq 40%

The pharmacokinetics of valsartan in HF patients were examined following a single dose (Protocol 102) and following twice a day (Every 12 h) multiple dose regimen (Protocol 105). The mean pharmacokinetic parameters of valsartan in HF patients following 10-160 mg single doses (Protocol 102) are summarized in Table 2-2.

Table 2-2. Mean pharmacokinetic parameters of valsartan (Study 102)

Dose (mg)	N	C _{max} (ng/mL)	T _{max} * (hr)	AUC(0-24) (ngxhr/mL)	Terminal Half-life (hr)**
10	5	280 (24)	3 (2-6)	2379 (16)	10.1
20	2	684 (22)	3 (2-3)	6381 (43)	8.9
40	3	843 (36)	2 (1-8)	7147 (20)	7.2
80	4	2147 (69)	3 (2-8)	21244 (89)	9.2
160	4	2773 (41)	6 (1-6)	37971 (66)	9.2

Values in parenthesis represent CV(%) for C_{max} and AUC, and range for T_{max}

*Median value; **Calculated from the mean plasma concentration-time data for each dose.

The pharmacokinetics of valsartan following twice daily dosing in Study 105 are shown in Table 2-3. The results of this study showed that the mean plasma valsartan AUC (0-24) and C_{max} linearly increased with dose. Inter-subject variability in the pharmacokinetic parameters was large.

Table 2-3. Pharmacokinetics of valsartan following twice daily dosing (Study 105)

Dose (mg)	C _{max} (ng/ml)	T _{max} * (hr)	C _{min} (ng/ml)	AUC(0-12) (ng.hr/ml)	T _{1/2} (hr)
40	1940 (971)	3	473 (313)	13119 (7220)	5.2 (1.9)
80	3951 (2290)	2.5	1050 (849)	25936 (15670)	6.5 (2.4)
160	6403 (3190)	3	1981 (1605)	43540 (25897)	6.6 (3.9)

* Median value

Mean (SD) steady-state pharmacokinetic parameters following multiple Q 12 h (BID) dosing to patients with HF are presented graphically in Figures 2-1 and 2-2 (N=18).

Figure 2-1. Mean \pm S.D. AUC (0-12) versus dose in CHF patients following multiple Q 12 h dosing (Study 105) (N=18)

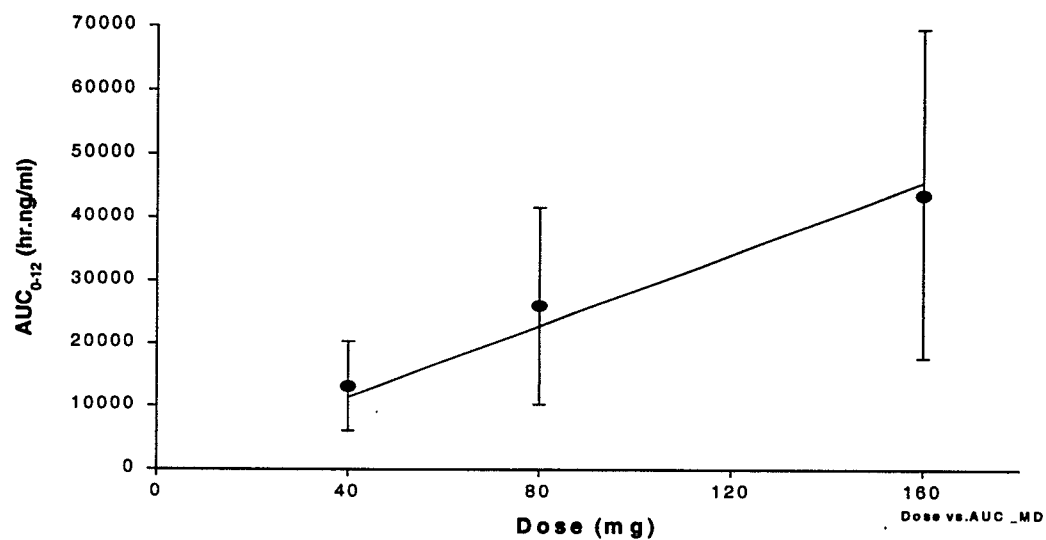
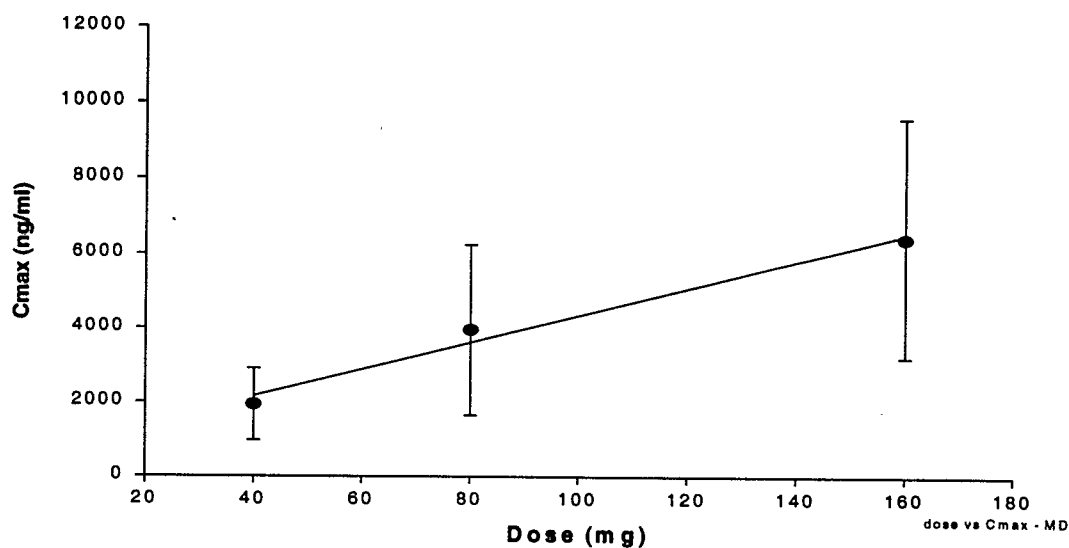


Figure 2-2. Mean \pm S.D. C_{max} versus dose in CHF patients following multiple Q 12 h dosing (Study 105) (N=18)



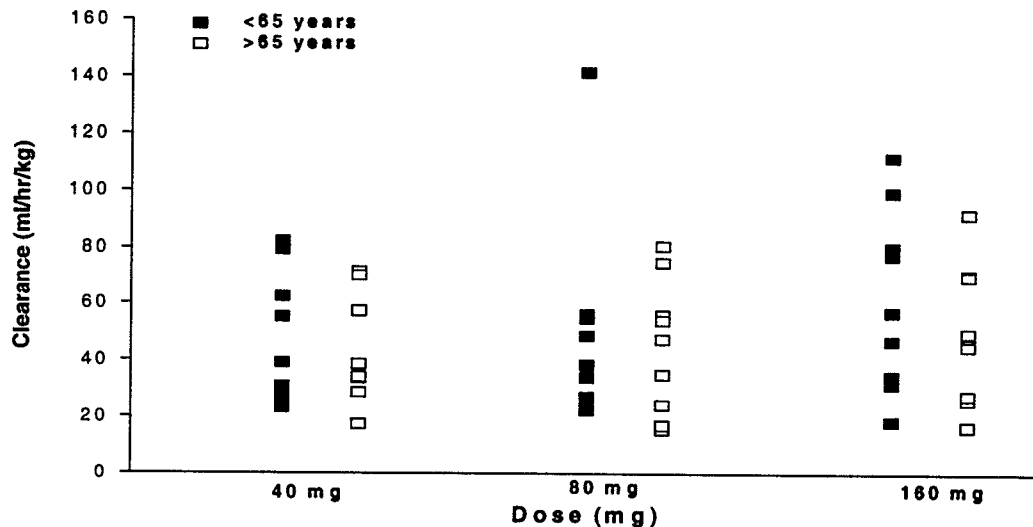
In addition to dose proportionality and linearity, the data was evaluated to examine if the clearance of valsartan was very different between <65 years old and >65 years old patients. Table 2-4 lists the exposure and clearance values in the two age groups.

Table 2-4. Exposure and clearance by age group (Study 105)

Dose	<65 years (N=9)		>65 years (N=9)	
	AUC ₍₀₋₁₂₎ ng.hr/ml	Clearance ml/hr/kg	AUC ₍₀₋₁₂₎ ng.hr/ml	Clearance ml/hr/kg
40 mg	11325 (5720)	47.4 (23.1)	14913 (8414)	41.0 (20.7)
80 mg	22250 (9668)	49.7 (36.7)	29622 (19944)	45.1 (23.8)
160 mg	36560 (20589)	62.1 (32.1)	50520 (29861)	49.4 (24.4)

A graphical presentation of individual clearance values adjusted to body weight is presented in Figure 2-3.

Figure 2-3. Individual clearance values adjusted to body weight (Study 105)



The conclusions from Study 105 were:

- Valsartan was well tolerated up to 160 mg twice a day by patients with CHF.
- The pharmacokinetics (AUC and C_{max}) of valsartan showed a linear and almost dose-proportional relationship in the dose range of 40 to 160 mg twice a day in patients with CHF.
- Valsartan clearance appeared to be less in CHF patients with slight accumulation than that in healthy subjects.
- Age did not seem to have an effect on the clearance of valsartan in patients with CHF.

2.3. Summary of clinical pharmacology and conclusions

The clinical pharmacology conclusions from the two clinical pharmacology studies (Protocol 102: single dose study; and Protocol 105: multiple dose study) performed in heart failure (HF) patients are presented below.

- Mean plasma aldosterone concentrations and PCWP decreased in patients treated with valsartan single dose compared to those treated with placebo.
- Following a single dose, there was no apparent trend between plasma valsartan concentration and PRA, Ang II concentration, aldosterone concentration, PCWP, or CO.

- There was no apparent association between neurohormonal variables (PRA, plasma Ang II and aldosterone concentration) and hemodynamic variables (PCWP and CO), based on the placebo adjusted mean change from baseline data following a single dose.
- Steady-state pharmacokinetics (AUC and Cmax) of valsartan showed a linear and almost proportional relationship in the dose range of 40 to 160 mg twice a day (Q 12 h) in patients with HF.
- Valsartan clearance appears to be less in HF patients with slight accumulation than that in healthy subjects (1.7 vs. 1.3) when dosed at 40 to 160 mg twice daily compared with the normal regimen recommended (once daily) for the treatment of hypertension.
- Age did not seem to have an effect on the clearance of valsartan in HF patients.

3. Adequate and Well-Controlled Efficacy Studies

A total of 5 studies are presented, which are considered to be adequate and well-controlled, according to the following criteria:

- the study objectives and method of analysis were stated in the protocol and study report
- the study design permitted valid comparison with a control situation
- the method of patient selection adequately assured they had the condition being studied
- treatment assignment minimized bias to assure comparability of treatment groups
- adequate measures were taken to minimize bias by subjects, observers and data analysts
- the measures used to assess the subject's response were well-defined and reliable
- the analysis of study results was adequate to assess the effects of the drug

Studies 104, 106 and 107 were the placebo-controlled studies, Study 103 was placebo- and active-controlled, and Study 110 was active-controlled. These were all multi-center, double-blind, multiple dose, randomized, parallel group studies in adult patients (ie 18-80 years of age in Studies 103 and 104; ≥ 18 years of age in Studies 106, 107 and 110) with chronic stable HF (NYHA Class II-IV except Study 110 which included Class II-III patients). Patients with significant cardiovascular diseases or recent episodes of significant cardiovascular events were excluded from these studies.

An overview of the major features of the adequate and well-controlled trials presented is given in Tables 3-1 and 3-2.

Table 3-1. Summary of adequate and well controlled studies (placebo-controlled)

Study	Purpose, population and design	Type of control	Treatment groups	DB treatment duration	Rand no of pts	Efficacy measures
103	Evaluate effects of valsartan on central hemodynamic assessments in pts with chronic, stable HF (NYHA Class II-IV, PCWP \geq 15 mmHg, -ACEI) MC, parallel, DB, randomized	Placebo Active (lisinopril)	Val 40 mg BID Val 80 mg BID Val 160 mg BID Placebo Lis 5/10 mg OD	4 weeks	116	Primary: Central hemodynamic assessments Secondary: Plasma neurohormones
104	Evaluate effects of valsartan on central hemodynamic assessments in pts with chronic, stable HF (NYHA Class II-IV, LVEF \leq 40%, PCWP $>$ 15 mmHg, +ACEI) MC, parallel, DB, randomized	Placebo	Val 80 mg BID Val 160 mg BID Placebo	4 weeks	83	Primary: Central hemodynamic assessments Secondary: Plasma neurohormones
106	Evaluate effects of valsartan on exercise capacity in pts with chronic, stable HF (NYHA Class II-IV, LVEF \leq 40%, +/-ACEI) MC, parallel, DB, randomized	Placebo	Val 40 mg BID Val 80 mg BID Val 160 mg BID Placebo	16 weeks	770	Primary: Maximal exercise tolerance test, Quality of Life Secondary: HF signs and symptoms, NYHA Class, LVEF
107 Val-HeFT	Evaluate effects of valsartan on morbidity/mortality in pts with chronic, stable HF (NYHA Class II-IV, LVEF $<$ 40%, LVDD $>$ 2.9cm/m ² , +/-ACEI) MC, parallel, DB, randomized	Placebo	Val 40-160 mg BID forced titration Placebo	24-36 months	5010	Primary: Morbidity/mortality, 6 min walk exercise test (substudy) Secondary: HF signs and symptoms, NYHA Class, Quality of life, LVEF, LVIDD, Plasma neurohormones

ACEI=angiotensin converting enzyme inhibitor
 AVPD=atrioventricular plane displacement
 DB=double-blind
 Enal=enalapril
 HF=heart failure
 lis=lisinopril
 LVEF=left ventricular ejection fraction
 LVIDD=left ventricular internal diameter in diastole
 MC=multicenter
 NYHA=New York Heart Association
 pts=patients
 PCWP = pulmonary capillary wedge pressure
 rand=randomized
 Val=valsartan
 ValHeFT=Valsartan Heart Failure Trial

Table 3-2. Summary of adequate and well controlled studies (active-controlled)

[illegible]

3.1. Hemodynamic and Neurohormone Studies (103 and 104)

3.1.1. Trial Designs

Study 103 was a placebo- and active-controlled trial to assess the cardiac hemodynamic effects of 3 doses of valsartan in patients with chronic stable CHF. Patients were allowed to receive standard HF background therapy with the exception of ACE inhibitors which were prohibited 6 months prior to enrollment and throughout the duration of the trial. Eligible patients were randomized to receive valsartan 40 mg BID, valsartan 80 mg BID, valsartan 160 mg BID, placebo BID for four weeks, or lisinopril 5 mg once daily for 7 days followed by 10 mg once daily for three weeks, in a randomization ratio of 2:2:2:2:1. One day prior to dosing, eligible patients were admitted to an intensive care unit and right heart catheterization using a Swan-Ganz catheter was performed. Following a 2-4 week drug-free run-in period, patients were eligible to receive randomized study medication if the two initial mean PCWP values on day -1 were both ≥ 15 mm Hg, and were within 10% of each other. On the day of dosing, baseline hemodynamic measurements were done and randomized study medication was administered. Hemodynamic measurements and plasma neurohormone levels were done up to 12 hours following the first dose of study medication and at Hour 0 and up to 12 hours following dosing on day 28 of dosing. Digitalis and nitroglycerin administration were prohibited within 12 hours of hemodynamic measurements and the patient's diuretic dose was held on the day prior to and the day of the hemodynamic measurements at day 0 and day 28. A total of 145 patients were enrolled in the trial; 116 patients were randomized to valsartan, lisinopril, or placebo; and 103 patients completed the trial. A total of 113 patients were included in the primary efficacy analysis of central hemodynamics.

Study 104 was a placebo-controlled, dose response trial to determine the acute and chronic central hemodynamic effects of valsartan in patients with symptomatic CHF. The study included patients who were on a fixed regimen of a therapeutic dose of an ACE inhibitor and a fixed regimen of digitalis and diuretics (if applicable) for at least four weeks prior to study entry. Following a two-week single-blind placebo run-in period, patients had right heart catheterization performed with a Swan-Ganz catheter in order to provide central hemodynamic measurements. The initial two mean PCWP values were required to be ≥ 15 mm Hg. The following morning, patients were required to have two consecutive mean PCWP values with less than 10% variability. Patients were randomized to valsartan 80 mg BID, valsartan 160 mg BID, or placebo. On the days when hemodynamic measurements were obtained, the patient's usual diuretic and ACE inhibitor doses were withheld for the duration of the 12-hour hemodynamic measurement period. A dose of lisinopril was given following the 0-hour hemodynamic measurements. The dose of lisinopril to be administered was determined by the dose of ACE inhibitor being taken chronically by the patient; i.e. a single dose of 10 mg for patients taking low dose ACE inhibitor and a single dose of 20 mg for patients taking high dose ACE inhibitors. Patients were treated with study medication for four weeks and then had repeat right heart catheterization and central hemodynamic

measurements. Neurohormonal measurements were also made on day 0 and day 28. A total of 143 patients receiving therapeutic doses of an ACE inhibitor were enrolled in the trial; 83 patients were randomized and 74 patients completed the trial. A total of 68 patients were included in the primary efficacy analysis of central hemodynamics.

3.1.2. Hemodynamic Endpoint Results

Studies 103 and 104 enrolled patients with chronic stable HF and baseline PCWP ≥ 15 mmHg. Patients in Study 103 were not treated with background ACE inhibitor therapy; patients in Study 104 were required to be treated with therapeutic doses of ACE inhibitors. In Study 104, all patients had their usual dose of ACE inhibitor held on the morning of hemodynamic monitoring and were administered a dose of lisinopril following the 0-hour hemodynamic assessments. Hemodynamic assessments were made pre-dose, and up to 12 hours after dosing on Day 0 and Day 28 of dosing. In studies 103 and 104, the primary endpoint was mean change from baseline in PCWP at 4-8 hours after study drug dosing and at 12 hours after study drug dosing on Day 28.

Pulmonary capillary wedge pressure

The placebo-subtracted mean differences for the valsartan treatment groups at the primary time points on Day 28, derived from the analysis of covariance for change from baseline in mean pulmonary capillary wedge pressure (PCWP), are presented in Table 3-3 and Figure 3-1.

Table 3-3. Placebo-subtracted mean change from baseline (Day 0, hour 0) in PCWP (mmHg) at hour 0, peak and trough, Day 28, Studies 103 and 104

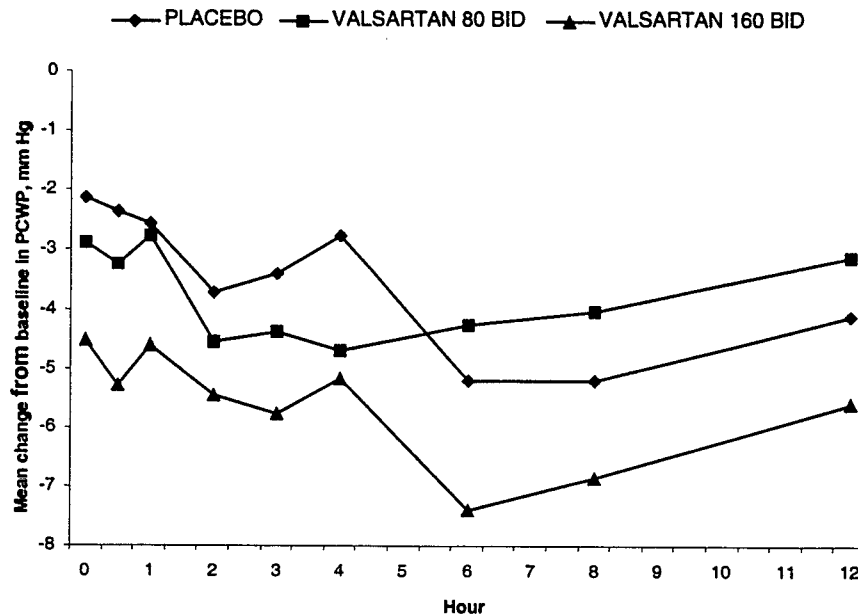
Study Treatment group	Hour 0		Peak (4-8 hours)		Trough (12 hours)	
	Diff vs. placebo ^a	(CI) p-value	Diff vs. placebo ^a	(CI) p-value	Diff vs. placebo ^a	(CI) p-value
Study 103						
Valsartan 40 mg BID	n=20 -6.42 (-11.34,-1.50) 0.002*		n=20 -5.99 (-11.28,-0.70) 0.007*		n=20 -7.51 (-13.22,-1.80) 0.002*	
Valsartan 80 mg BID	n=22 -1.26 (-6.01,3.48) 0.518		n=21 -2.78 (-7.95,2.39) 0.194		n=21 -4.47 (-10.06,1.13) 0.055	
Valsartan 160 mg BID	n=25 -5.89 (-10.48,-1.31) 0.002*		n=25 -6.88 (-11.81,-1.95) 0.001*		n=25 -7.46 (-12.80,-2.12) 0.001*	
Lisinopril 5/10 mg OD	n=14 -2.66 (-7.45,2.13) 0.273		n=14 -2.44 (-7.62,2.74) 0.352		n=14 -5.18 (-10.80,0.44) 0.071	
Study 104						
Valsartan 80 mg BID	n=22 -0.73 (-4.64,3.18) 0.669		n=21 0.05 (-3.86,3.96) 0.977		n=21 1.00 (-2.85,4.85) 0.551	
Valsartan 160 mg BID	n=22 -2.40 (-6.31,1.52) 0.164		n=22 -1.83 (-5.71,2.05) 0.281		n=22 -1.46 (-5.29,2.36) 0.381	

CI = confidence interval; CI for Study 104: 97.5%; CI for Study 103: 98.3% for valsartan contrasts, 95% for lisinopril

^aDifference=active treatment (valsartan or lisinopril) least squares mean (LSM) change from BL minus placebo LSM change from BL; for placebo: n=23 to 24 for Study 103, n=25 to 26 for Study 104

* Indicates statistical significance at the level of 0.017 (p<0.017), valsartan vs. placebo

Figure 3-1. Mean change from baseline in pulmonary capillary wedge pressure (PCWP, mm Hg), day 28, Study 104



In Study 103, at both primary timepoints and at all other timepoints (except hour 4 for valsartan 40 mg BID), statistically significant reductions in mean PCWP compared to placebo were observed for valsartan 40 mg BID (5.4-7.5 mm Hg placebo subtracted) and valsartan 160 mg BID (5.2-7.6 mm Hg placebo subtracted) on Day 28.

In Study 104, reductions in PCWP compared to placebo ranged from 0.9 to 2.9 mm Hg (placebo subtracted) for valsartan 160 mg BID, but were not statistically significant on Day 28, although statistically significant reductions in PCWP with the 160 mg BID dose were observed at several timepoints after the first dose on Day 0.

Diastolic pulmonary artery pressure

In Study 103, decreases in diastolic pulmonary artery pressure (DPAP) were observed 12 hours post-dose on Day 28 for all three valsartan treatment groups. Mean changes from baseline were -5.5, -3.2, and -3.5 mm Hg for valsartan 40 mg BID, 80 mg BID, and 160 mg BID, respectively, and -0.2 and 0.6 mmHg for lisinopril 5/10 mg OD and placebo, respectively. No formal statistical analyses were carried out for DPAP.

In Study 104, the placebo-subtracted mean differences for the valsartan treatment groups at the primary time points, on Day 28, derived from the analysis of covariance for change from baseline in mean diastolic pulmonary artery pressure are presented in Table 3-4 and Figure 3-2.

Table 3-4. Placebo-subtracted mean change from baseline in diastolic pulmonary artery pressure (DPAP, mmHg) at peak and trough, Day 28, Study 104

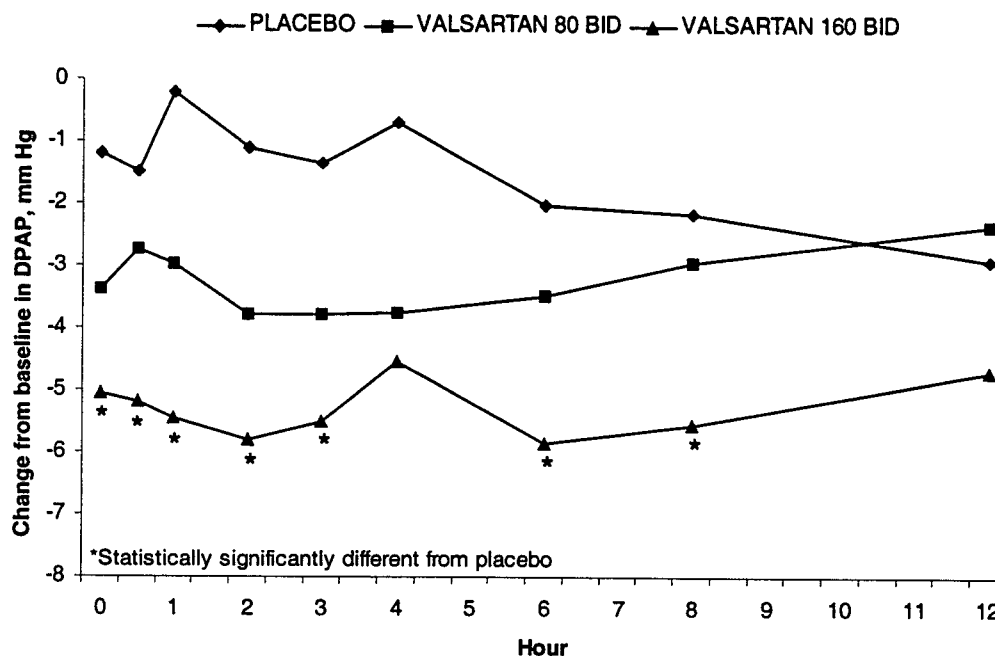
Treatment group	Day 28 Hour 0			Day 28 Peak (mean of 4-8 hours)			Day 28 Trough (12 hours)		
	N	Diff vs. plc ^a	(CI) p-value	N	Diff vs. plc ^a	(CI) p-value	N	Diff vs. plc ^a	(CI) p-value
Valsartan 80 mg BID	24	-2.19	(-5.68,1.29) 0.153	24	-1.92	(-5.01,1.17) 0.158	24	0.59	(-2.90,4.08) 0.700
Valsartan 160 mg BID	23	-3.85	(-7.31,-0.38) 0.013#	23	-3.66	(-6.73,-0.59) 0.008#	23	-1.77	(-5.24,1.70) 0.246

plc=placebo; CI = 97.5%confidence interval

^aDifference=valsartan least squares mean (LSM) change from baseline minus placebo LSM change from baseline; for placebo: n=27

Indicates statistical significance at the level of 0.025 (p<0.025)

Figure 3-2. Mean change from baseline in diastolic pulmonary artery pressure (DPAP, mmHg), day 28, Study 104



At the primary timepoint of peak (4-8 hours) and at all other timepoints (except hours 4 and 12) on Day 28, statistically significant reductions in mean pulmonary artery diastolic pressure (DPAP) compared to placebo were observed for valsartan 160 mg BID (1.8-5.3 mmHg placebo-subtracted). The greatest reduction in DPAP for the 80 mg BID dose was 3.1 mmHg (placebo-subtracted), but at no timepoint was there a statistically significant difference versus placebo.

Cardiac output

In Study 103, treatment with valsartan resulted in an increase in cardiac output (CO). The placebo-subtracted mean differences in CO for the valsartan treatment groups at time point 4 to 8 hours on Day 28 ranged from 0.69 L/min to 0.88 L/min. All valsartan effects were statistically different from placebo. The placebo-subtracted mean differences in CO at 12 hours after dosing on Day 28 ranged from 0.76 L/min for valsartan 40 mg BID to 1.09 L/min for valsartan 160 mg BID, with both the 80 mg BID and the 160 mg BID doses being statistically significantly different from placebo.

In Study 104, there were no consistent clinically or statistically significant acute or chronic changes over the 12 hour hemodynamic monitoring periods for either valsartan treatment group compared to placebo for cardiac output.

Other central and peripheral hemodynamic assessments

In Studies 103 and 104, after 28 days of dosing, valsartan resulted in vasodilatory effects, as evidenced by decreases in right atrial, pulmonary arterial and systemic blood pressures, and systemic and pulmonary vascular resistances, as well as beneficial effects on stroke volume index. There was a great deal of variability in these assessments, and only isolated time points achieved statistically significant differences from placebo.

Summary of hemodynamic endpoints

Acute and chronic (after 4 weeks) central and peripheral hemodynamic effects were observed after dosing with valsartan, given with or without chronic therapy with an ACE inhibitor. In general, a greater vasodilatory effect was observed on Day 0 than after chronic dosing. In Study 104, valsartan 160 mg BID in addition to chronic ACE inhibitor therapy produced sustained hemodynamic effects after four weeks of dosing. The data from Study 104 suggests that the hemodynamic effects are greater with the 160 mg BID dose than lower doses.

3.1.3. Neurohormonal Endpoint Results

The effects after 28 days of dosing with valsartan were assessed for plasma renin activity (PRA), aldosterone, angiotensin II, norepinephrine, and atrial peptide activity (APEP) in one or both of the 28-day hemodynamic Studies 103 and 104. Chronic effects of valsartan on plasma norepinephrine and brain natriuretic peptide (BNP) were assessed in the morbidity and mortality Study 107 (Section 3.2.3.)

Short-term effects after 28 days of dosing (Studies 103 and 104)

Baseline neurohormonal values

Table 3-5 presents the baseline mean values for PRA, aldosterone, angiotensin II (Studies 103 and 104) and Table 3-6 presents the mean baseline values for norepinephrine and APEP (Study 104).

Table 3-5. Mean baseline (day 0, hour 0) values for plasma renin activity (PRA, ng/mL/h), aldosterone (Aldo, ng/dL^a, pg/mL^b), angiotensin II (Ang II, pmol/mL^a, pg/mL^b), Studies 103 and 104¶

Study Treatment group	PRA		Aldo		Ang II	
	N	BL Mean (SD)	N	BL Mean (SD)	N	BL Mean (SD)
Study 103						
Valsartan 40 mg BID	19	1.37 (2.52)	19	23.11 (21.97)	19	19.21 (40.68)
Valsartan 80 mg BID	21	0.73 (0.81)	21	13.86 (8.14)	21	6.47 (5.26)
Valsartan 160 mg BID	24	2.18 (7.14)	24	13.74 (8.87)	24	12.75 (32.96)
Lisinopril 5/10 mg OD	14	1.64 (2.12)	14	20.07 (16.82)	14	7.20 (5.41)
Placebo	24	1.63 (3.11)	22	27.43 (33.53)	24	11.80 (19.88)
Study 104						
Valsartan 80 mg BID	27	5.04 (8.19)	27	103.87 (125.29)	26	5.07 (5.80)
Valsartan 160 mg BID	27	7.15 (11.52)	27	97.31 (72.47)	25	4.47 (5.38)
Placebo	28	5.26 (8.96)	28	93.90 (91.89)	26	6.80 (17.87)

^aStudy103 ^bStudy 104 BL=baseline; SD=standard deviation

¶Includes all randomized patients with a baseline value but not necessarily with respective post-baseline or endpoint value

Table 3-6. Mean baseline (day 0, hour 0) values for plasma norepinephrine (NE, pg/mL) and plasma atrial peptide activity (APEP, pg/mL), Study 104¶

Treatment group	NE		APEP	
	N	BL Mean (SD)	N	BL Mean (SD)
Valsartan 80 mg BID	27	320.59 (147.52)	27	402.37 (324.34)
Valsartan 160 mg BID	27	410.96 (303.01)	27	406.00 (262.42)
Placebo	28	274.43 (183.71)	28	330.43 (338.68)

BL=baseline; SD=standard deviation

¶Includes all randomized patients with a baseline value but not necessarily with respective post-baseline or endpoint value

Aldosterone

Table 3-7 presents placebo-subtracted changes from baseline in plasma aldosterone at hour 0, peak and trough time points on Day 28 for Studies 103 and 104.

Table 3-7. Placebo-subtracted mean change from baseline (Day 0, hour 0) in plasma aldosterone (ng/dL^a, pg/mL^b) at hour 0, peak and trough, Day 28, Studies 103 and 104

Study Treatment group	Hour 0		Peak (4 ^a /6 ^b hours)		Trough (12 hours)	
	Diff vs. placebo ^x	(CI) p-value	Diff vs. placebo ^x	(CI) p-value	Diff vs. placebo ^x	(CI) p-value
Study 103						
Valsartan 40 mg BID	n=19 -5.08 (-12.89,2.73) 0.117		n=19 -10.61 (-18.39,-2.82) 0.001*		n=19 -6.00 (-12.76,0.76) 0.034	
Valsartan 80 mg BID	n=21 -0.75 (-9.00,7.50) 0.825		n=19 -5.37 (-15.25,4.51) 0.189		n=20 -3.47 (-10.65,3.71) 0.242	
Valsartan 160 mg BID	n=24 -0.73 (-8.99,7.54) 0.831		n=23 -7.37 (-15.64,0.90) 0.033		n=24 -5.99 (-13.17,1.19) 0.045	
Lisinopril 5/10 mg OD	n=14 -8.58 (-15.46,-1.69) 0.015†		n=14 -12.47 (-19.30,-5.63) <0.001†		n=14 -7.88 (-13.84,-1.91) 0.010†	
Study 104						
Valsartan 80 mg BID	n=22 -49.82 (-81.81, -17.84) 0.001#		n=22 -50.08 (-85.28, -14.88) 0.002#		n=22 -8.16 (-32.86, 16.55) 0.450	
Valsartan 160 mg BID	n=23 -50.87 (-81.79, -19.95) <0.001#		n=22 -44.13 (-78.49, -9.78) 0.005#		n=22 -26.92 (-51.03, -2.82) 0.013#	

CI = confidence interval; CI for protocol 104: 97.5%; CI for protocol 103: 98.3% for valsartan contrasts, 95% for lisinopril

* Indicates statistical significance at the level of 0.017 (p<0.017), valsartan vs. placebo

† Indicates statistical significance at the level of 0.05 (p<0.05), lisinopril vs. placebo

Indicates statistical significance at the level of 0.025 (p<0.025), valsartan vs. placebo

^aProtocol 103

^bProtocol 104

^xDifference=active treatment (valsartan or lisinopril) least squares mean (LSM) change from BL minus placebo LSM change from BL; for placebo: n=21 to 22 for Study 103 and n=26 to 27 for 104

In Study 103, placebo-subtracted change from baseline in plasma aldosterone decreased for all valsartan treatment groups and the lisinopril treatment group at the 0 hour, peak, and trough time points on Day 28. There were statistically significant differences between valsartan 40 mg BID and placebo at peak on Day 28 and between lisinopril and placebo at all three time points on Day 28. For comparisons between valsartan 160 mg BID and placebo at peak and

trough on Day 28 and between valsartan 40 mg BID at trough on Day 28, p-values < 0.05 were observed, but these differences were not statistically significant.

In Study 104, decreases in placebo-subtracted change from baseline in plasma aldosterone were observed for both valsartan treatment groups at all 3 time points on Day 28. There were statistically significant differences between valsartan 160 mg BID and placebo at all 3 time points on Day 28 and between valsartan 80 mg BID and placebo at Hour 0 and peak on Day 28. Statistically significant treatment-by-baseline interactions were also observed at all three Day 28 time points, with greater decreases in aldosterone observed for valsartan patients with larger baseline values.

Plasma Norepinephrine

Table 3-8 presents placebo-subtracted changes from baseline in plasma norepinephrine at hour 0, peak and trough time points on Day 28.

Table 3-8. Placebo-subtracted mean change from baseline (Day 0, hour 0) in plasma norepinephrine (pg/mL) at hour 0, peak, and trough, Day 28, Study 104

Treatment group	Hour 0		Peak (6 hours)		Trough (12 hours)	
	Diff vs. placebo ^x	(CI) p-value	Diff vs. placebo ^x	(CI) p-value	Diff vs. placebo ^x	(CI) p-value
Valsartan 80 mg BID	-14.10	n=22 (-73.87, 45.66) 0.588	11.83	n=22 (-69.49, 93.16) 0.738	-1.43	n=22 (-87.87, 85.01) 0.970
Valsartan 160 mg BID	-42.69	n=22 (-101.44, 16.06) 0.100	-76.69	n=22 (-156.64, 3.25) 0.031	-75.50	n=22 (-160.91, 9.90) 0.046

CI = 97.5% confidence interval

Indicates statistical significance at the level of 0.025 (p<0.025), valsartan vs. placebo

^xDifference=valsartan LSM change from BL minus placebo LSM change from BL; for placebo: n=26 to 27.

In Study 104, placebo-subtracted change from baseline in plasma norepinephrine decreased for valsartan 160 mg BID at all 3 time points on Day 28, and for valsartan 80 mg BID at Hour 0 and at peak on Day 28. For the comparisons between valsartan 160 mg BID and placebo, p-values < 0.05 were observed at peak and trough on Day 28, but these differences were not statistically significant. Baseline mean plasma norepinephrine levels were higher in the valsartan 160 mg BID treatment group compared to the other treatment groups; and statistically significant treatment-by-baseline interactions were observed at peak and trough on Day 28, with greater between-treatment differences occurring for patients with larger baseline values.

Plasma Angiotensin II

In Study 103, increases in placebo-subtracted change from baseline for plasma angiotensin II were observed in all valsartan treatment groups at all three time points on Day 28 with the exception of valsartan 40 mg BID at trough. Valsartan 80 mg BID was statistically significantly different from placebo at trough. For the comparison of valsartan 160 mg BID versus placebo, a p-value < 0.05 was observed at peak on Day 28, but the difference was not statistically significant. A statistically significant treatment-by-baseline interaction was also observed at trough.

In Study 104, which compared valsartan to placebo in patients receiving ACE inhibitors, no statistically significant treatment differences for plasma angiotensin II were found between valsartan and placebo at any analysis time point on Day 28. This may be due to the co-administration of an ACE inhibitor.

Plasma atrial peptide activity

In Study 104, placebo-subtracted change from baseline in plasma atrial peptide decreased for both valsartan groups at all 3 time points on Day 28, but these differences from placebo were not statistically significant. Baseline mean plasma atrial peptide activity was lower for placebo than for the valsartan treatment groups.

3.2. Val-HeFT - Morbidity and Mortality Study (107)

3.2.1. Purpose

The Valsartan Heart Failure Trial (Val-HeFT) was undertaken to determine whether the angiotensin receptor blocker (ARB), valsartan, could further reduce morbidity and mortality in patients already receiving pharmacologic therapy considered optimal by their physicians. Val-HeFT is the first large-scale trial to evaluate an ARB added to an ACE inhibitor.

3.2.2. Design

Study 107 (Val-HeFT), a multi-country, forced titration study, included patients with LVEF <40% on echocardiography and left ventricular internal diameter in diastole (LVIDD) >2.9 cm/m² on echocardiography. Patients had to be on a stable dosage regimen of their HF medication (diuretics, ACE inhibitors, digoxin, hydralazine hydrochloride, nitrates, and beta blockers) for at least two weeks prior to study entry and through the 2 to 4 week single-blind placebo run-in period during which qualification procedures were performed. Patients with diseases that might limit survival were excluded. Eligible patients were randomized to valsartan 40 mg BID or placebo, stratified by baseline β -blocker therapy. Study medication was force-titrated up to a maximum dose of 160 mg BID at two week intervals based on prespecified criteria. The double-blind treatment duration was targeted at 24-36 months. A

total of 5984 patients were enrolled in the trial; 5010 patients were randomized, 4953 patients completed the trial, and 4223 patients completed study treatment (i.e. were not permanently withdrawn from study medication during the trial). A total of 5010 patients were included in the primary efficacy analysis of morbidity and mortality.

The study was designed with two primary end points: time to death and time to first morbid event defined as death, sudden death with resuscitation, hospitalization for heart failure, or administration of intravenous inotropic or vasodilator drugs for four hours or more without hospitalization. Secondary cardiovascular outcomes included time to first occurrence of a morbid event other than death, time to hospitalization for CHF (first occurrence), time to cardiovascular-related death. Other secondary variables included change from baseline to end point (last available observation post-baseline) in ejection fraction, NYHA functional class, quality of life scores, and signs and symptoms of heart failure.

Statistical analysis was performed at an overall significance of 0.05, adjusted for the two primary end points. Each primary end point was tested at a two-sided significance of 0.02532 based on the Dunn-Sidak inequality: $\alpha' = 1 - (1 - \alpha)^{1/2}$. Significance level for time to death was further adjusted for five biannual interim analyses according to the O'Brien-Flemming alpha-spending function. Therefore, the final analysis for time to death was performed at a two-sided significance level of 0.02. Sample size was based on the time to death end point. Number of patient deaths required to detect a 20 percent reduction in the placebo death rate (estimated at 12 percent per year) with a 90 percent power, was calculated to be 906. Enrollment of 2500 patients per treatment arm was planned.

Between-treatment comparisons for the primary end points were performed using a log-rank test. Estimation of effect size utilized a Cox regression model with pre-specified baseline covariates, including NYHA Class, ejection fraction (above and below median), etiology (ischemic and nonischemic), age (above and below 65 years), ACE inhibitor use, and beta-blocker use. Confidence intervals of 98% and 97.5% were calculated for mortality and morbidity, respectively. To estimate effect sizes in secondary end-points and subgroups, relative risks with 95 percent confidence intervals were calculated using the Cox regression model.

Patient baseline characteristics are listed in Table 3-9a and 3-9b.

Table 3-9a. Baseline demographics (Randomized population)

Parameter	Valsartan N=2511	Placebo N=2499	Total N=5010
Sex n (%)			
Male	2007 (79.9)	2000 (80.0)	4007 (80.0)
Female	504 (20.1)	499 (20.0)	1003 (20.0)
Race n (%)			
Caucasian	2255 (89.8)	2271 (90.9)	4526 (90.3)
Black	182 (7.2)	162 (6.5)	344 (6.9)
Oriental/other	74 (2.9)	66 (2.6)	140 (2.8)
Mean age (years) (SD)	62.4 (11.1)	63.0 (11.0)	62.7 (11.1)
Range	18.0-96.0	20.0-92.0	18.0-96.0
Age group: n (%)			
< 65 years	1367 (54.4)	1293 (51.7)	2660 (53.1)
≥ 65 years	1144 (45.6)	1206 (48.3)	2350 (46.9)
Mean height (cm) (SD)	171.1 (9.2)	171.2 (9.3)	171.1 (9.2)
Range	111.8-199.3	128.0-203.0	111.8-203.0
Mean weight (kg) (SD)	79.5 (15.5)	78.7 (15.1)	79.1 (15.3)
Range	36.0-158.6	39.5-149.5	36.0-158.6
Mean sitting SBP (mmHg) (SD)	123.5 (18.4)	124.1 (18.6)	123.8 (18.5)
Range	77.5-214.5	81.0-207.0	77.5-214.5
Mean sitting DBP (mmHg) (SD)	75.5 (10.5)	75.6 (10.7)	75.5 (10.6)
Range	37.0-134.0	48.0-117.0	37.0-134.0
Sitting pulse rate (bpm) (SD)	73.2 (12.6)	73.5 (12.7)	73.4 (12.6)
Range	40.0-130.0	40.0-126.0	40.0-130.0

SD = Standard deviation; SPB = Systolic blood pressure; DPB = Diastolic blood pressure; bpm = Beats per minute

The two treatment groups were comparable at baseline in duration of CHF, NYHA classification, CHF etiology or in use of background therapy for CHF. The majority of patients had a NYHA classification of II or III with just under two-thirds with Class II. CHF etiology was mostly either coronary heart disease or idiopathic cardiomyopathy. Most patients used ACE inhibitors, diuretics and digoxin as background therapy for CHF. Around one third of the patients used beta blockers and one in ten patients used amiodarone or calcium channel blockers.

Table 3-9b. NYHA classification, CHF etiology and use of CVS-related medication (Randomized patients)

Parameter		Valsartan N=2511	Placebo N=2499	Total N=5010
NYHA classification: n (%)	I	2 (0.1)	3 (0.1)	5 (0.1)
	II	1560 (62.1)	1535 (61.4)	3095 (61.8)
	III	907 (36.1)	906 (36.3)	1813 (36.2)
	IV	42 (1.7)	55 (2.2)	97 (1.9)
Etiology: n (%)	Coronary heart disease	1446 (57.6)	1419 (56.8)	2865 (57.2)
	Idiopathic cardiomyopathy	780 (31.1)	780 (31.2)	1560 (31.1)
	Hypertension	154 (6.1)	183 (7.3)	337 (6.7)
	Other	131 (5.2)	117 (4.7)	248 (5.0)
Mean duration of congestive heart failure (months) (SD)		51.2 (52.0)	51.2 (50.3)	51.2 (51.2)
Range		2.0-660.0	1.0-420.0	1.0-660.0
Use of CVS-related medication: n (%)	ACE inhibitors	2326 (92.6)	2318 (92.8)	4644 (92.7)
	Diuretics	2154 (85.8)	2128 (85.2)	4282 (85.5)
	Digoxin	1685 (67.1)	1689 (67.6)	3374 (67.3)
	Nitrates†	986 (39.3)	957 (38.3)	1943 (38.8)
	Beta-blockers	867 (34.5)	883 (35.3)	1750 (34.9)
	Amiodarone	322 (12.8)	332 (13.3)	654 (13.1)
	Calcium channel blockers	289 (11.5)	320 (12.8)	609 (12.2)

NYHA = New York Heart Association; SD= Standard deviation; CVS = Cardiovascular system

† Long and short acting

3.2.3. Primary Endpoint Results

Morbidity and Mortality

Two primary endpoints were evaluated in Study 107: mortality and morbidity (morbidity includes all cause mortality, sudden death with resuscitation, need for intravenous vasodilating or inotropic therapy for HF, and HF hospitalizations). Table 3-10 and Figures 3-3 and 3-4 present the results of the primary analyses, time to death and time to first morbid event. Table 3-11 presents the causes of mortality in the two treatment groups. Fig. 3-5 presents the Kaplan-Meier analysis for the CHF hospitalizations.

Table 3-10. Number and percent of first events, mortality and morbid events, Study 107

	Events N (%)		Hazard ratio‡ (95% CI)	p-value*
	Valsartan	Placebo		
	n=2511	n=2499		
Primary endpoints				
Mortality ¹	495 (19.7)	484 (19.4)	1.02 (0.90,1.15)	0.801
Morbidity ²	723 (28.8)	801 (32.1)	0.87 (0.78,0.96)	0.009†
Secondary endpoints				
Cardiovascular deaths	427 (17.0)	419 (16.8)	1.012 (0.884,1.158)	0.857
Non-fatal morbid events	367 (14.6)	486 (19.4)	0.725 (0.633, 0.830)	0.00001††
HF hospitalization	349 (13.9)	463 (18.5)	0.725 (0.631,0.833)	0.00001††
Sudden death with resuscitation	20 (0.8)	30 (1.2)	0.653 (0.371,1.150)	0.151
IV therapy	7 (0.3)	8 (0.3)	0.894 (0.324,2.469)	0.787

HF=heart failure; IV=intravenous; CI=confidence interval

¹Mortality endpoint represents all cause mortality during entire trial

²Morbidity endpoint is defined as the first event including all cause mortality

*Log rank test for time to first event

†Indicates valsartan statistically significantly different from placebo at level of 0.0253 (p<0.0253), adjusted for two primary endpoints

‡Hazard ratio=valsartan/placebo from Cox regression model

††Indicates statistically significant from placebo at level of 0.05, (p<0.05)

Table 3-11. Causes of mortality, Study 107

	Valsartan n=2511	Placebo n=2499
Mortality, N (%)	495 (19.7)	484 (19.4)
Cardiovascular mortality, N (%)	427 (17.0)	419 (16.8)
Sudden cardiac death	230 (9.2)	212 (8.5)
Sudden cardiac death with premonitory worsening HF	32 (1.3)	46 (1.8)
Heart failure	118 (4.7)	125 (5.0)
Acute myocardial infarction	18 (0.7)	10 (0.4)
Cardiovascular procedure	4 (0.2)	6 (0.2)
Other cardiovascular	25 (1.0)	20 (0.8)
Non-cardiovascular mortality, N (%)	64 (2.6)	60 (2.4)
Cancer	30 (1.2)	30 (1.2)
Other	34 (1.4)	30 (1.2)
Unclassified, N (%)	4 (0.2)	5 (0.2)

Figure 3-3. Kaplan-Meier curve of the primary variable of all cause mortality, Study 107

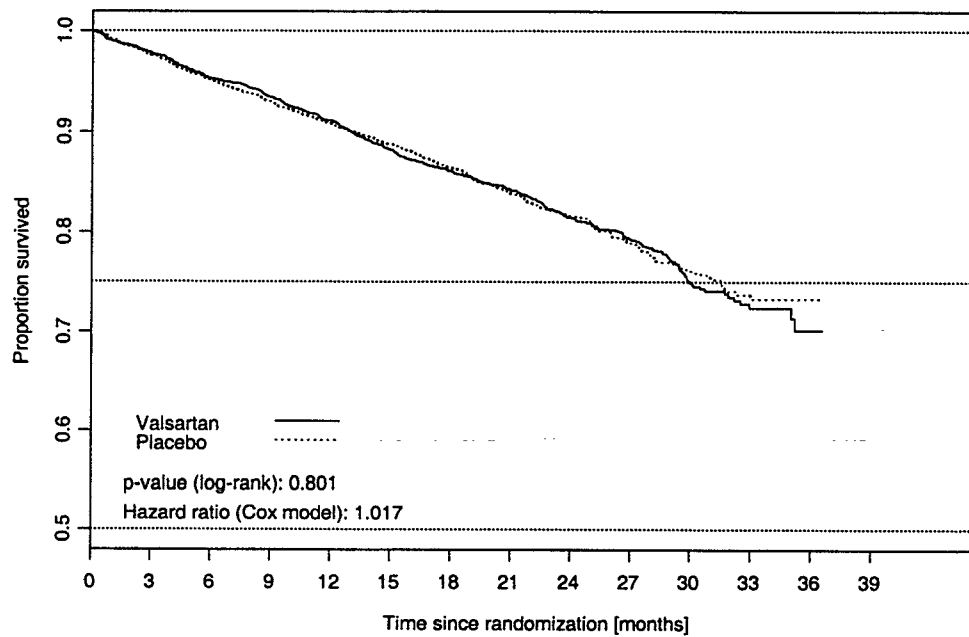


Figure 3-4. Kaplan-Meier curve of the primary efficacy variable of morbidity, Study 107

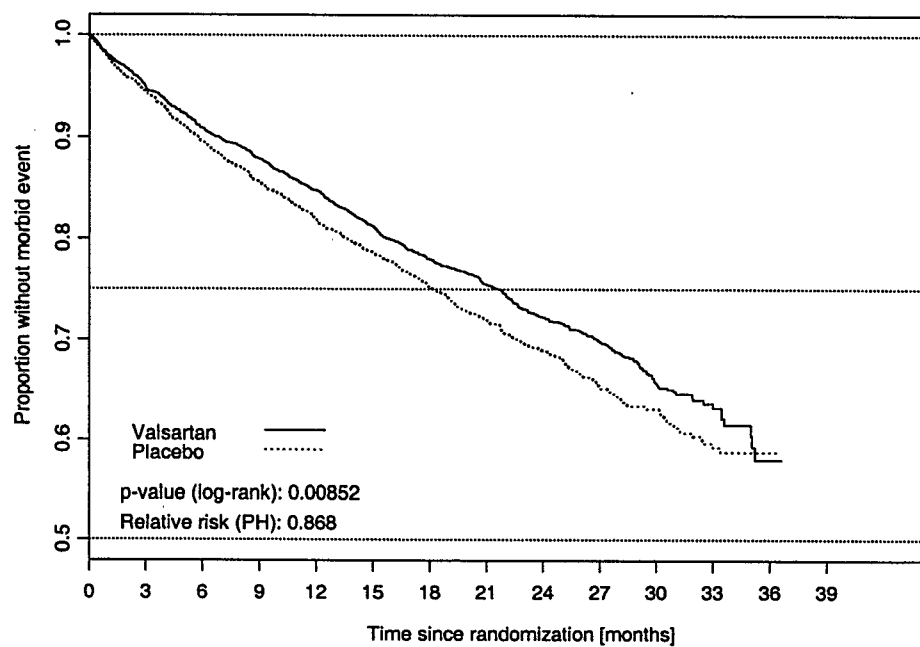
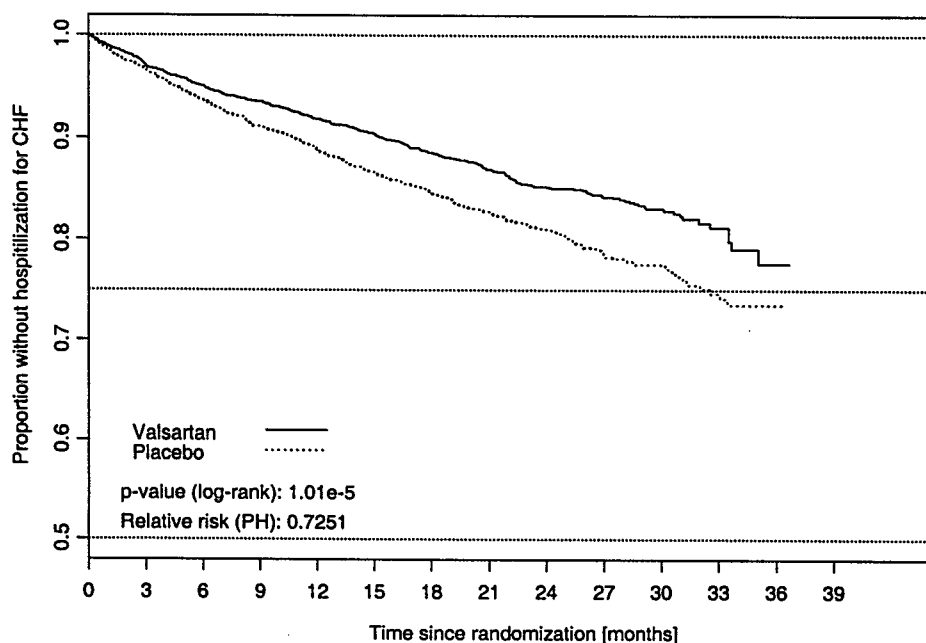


Figure 3-5. Kaplan-Meier curve of the secondary efficacy variable of CHF hospitalization, Study 107



Time to all-cause mortality was similar in the valsartan and placebo treatment groups. Cardiovascular mortality rate was similar in the two treatment groups. The adjudicated causes of both cardiovascular and noncardiovascular deaths were similar in the two treatment groups. The most frequent causes of death were sudden cardiac death (8.5-9.2%) and worsening heart failure (4.7-5.0%) in both treatment groups.

Time to first adjudicated morbid event, defined as all-cause mortality, and the nonfatal morbid events sudden death with resuscitation, treatment with intravenous vasodilating or inotropic therapy for worsening HF, and hospitalization for HF, was significantly delayed in the valsartan-treated patients compared to the placebo group ($p=0.009$). There was a 13.2% reduction in the combined risk with valsartan. The benefit appeared soon after randomization and increased for the duration of the trial. Most nonfatal morbid events were hospitalizations for worsening HF. The primary benefit on nonfatal morbidity was a 27.5% reduction in risk for time to first hospitalization for worsening HF ($p=0.00001$).

Subgroup analyses of morbidity and mortality

Tables 3-12 and 3-13 present all cause mortality in various subgroups and Tables 3-14 and 3-15 present morbidity in various subgroups in Study 107.

Table 3-12. Mortality in subgroups, Study 107

Subgroup	N		Deaths, %		Hazard ratio	95% CI	p-value
	Val n=2511	Plc n=2499	Val	Plc			
Age							
<65	1367	1293	15.2	15.0	1.001	(0.823,1.217)	0.871
≥65	1144	1206	25.1	24.0	1.041	(0.884,1.225)	0.638
Gender							
Male	2007	2000	20.7	20.1	1.022	(0.891,1.173)	0.609
Female	504	499	15.9	16.6	0.983	(0.722,1.338)	0.644
Race							
White	2255	2271	19.7	19.6	1.001	(0.877,1.142)	0.957
Black	182	162	20.3	14.2	1.479	(0.871,2.511)	0.127
Oriental/other	74	66	18.9	25.8	0.939	(0.429,2.056)	0.361
Countries							
Non US	1418	1414	18.9	18.5	1.027	(0.866,1.218)	0.868
US	1093	1085	20.8	20.5	1.015	(0.843,1.223)	0.853
Etiology of HF							
Ischemic	1446	1419	23.4	21.4	1.100	(0.942,1.285)	0.238
Nonischemic	1065	1080	14.6	16.7	0.889	(0.717,1.103)	0.212
NYHA							
I/II	1562	1538	15.5	14.4	1.088	(0.907,1.306)	0.345
III	907	906	25.7	26.3	0.951	(0.794,1.140)	0.589
IV	42	55	47.6	43.6	0.991	(0.528,1.861)	0.892
LVEF							
Below median	1211	1174	22.0	24.4	0.906	(0.766,1.071)	0.196
At or above median	1298	1325	17.6	14.9	1.192	(0.985,1.442)	0.085
Norepinephrine							
Below median	1071	1079	15.5	14.8	1.062	(0.854,1.320)	0.672
At or above median	1070	1081	23.6	23.5	1.001	(0.841,1.192)	0.968

ACEI=angiotensin converting enzyme inhibitor; BB=beta blocker; CI=confidence interval

LVEF=left ventricular ejection fraction; NYHA=New York Heart Association

Plc=placebo; Val=valsartan

*Indicates statistically significantly different from placebo at level of 0.05, p<0.05

Table 3-13. Mortality in subgroups: baseline background HF therapy, Study 107

Subgroup	N		Deaths, %		Hazard ratio	95% CI	p-value
	Val n=2511	Plc n=2499	Val	Plc			
ACEI Use							
No ACEI	185	181	17.3	27.1	0.669	(0.424,1.056)	0.0171*
ACEI	2326	2318	19.9	18.8	1.055	(0.925,1.203)	0.346
Beta Blocker Use							
No beta blocker	1644	1616	21.5	23.1	0.922	(0.797,1.067)	0.220
Beta blocker	867	883	16.4	12.5	1.357	(1.057,1.742)	0.018*
ACEI/Beta Blocker Use							
BB=no/ACEI=no	112	114	17.0	31.6	0.582	(0.330,1.025)	0.012*
BB=no/ACEI=yes	1532	1502	21.8	22.5	0.959	(0.824,1.116)	0.561
BB=yes/ACEI=no	73	67	17.8	19.4	0.807	(0.364,1.793)	0.578
BB=yes/ACEI=yes	794	816	16.2	11.9	1.421	(1.092,1.851)	0.009*
BB or ACEI or neither	1717	1683	21.3	23.0	0.924	(0.800, 1.066)	0.192

HF=heart failure; ACEI=angiotensin converting enzyme inhibitor; BB=beta blocker

CI=confidence interval; Plc=placebo; Val=valsartan

*Indicates statistically significantly different from placebo at level of 0.05, $p < 0.05$

Table 3-14. Morbidity in subgroups, Study 107

Subgroup	N		Morbidity, %		Hazard ratio	(95% CI)	p-value
	Val n=2511	Plc n=2499	Val	Plc			
Age							
<65	1367	1293	24.1	26.9	0.854	(0.734, 0.993)	0.093
≥65	1144	1206	34.4	37.6	0.882	(0.771, 1.010)	0.074
Gender							
Male	2007	2000	29.4	32.1	0.872	(0.779, 0.975)	0.053
Female	504	499	26.4	32.1	0.839	(0.666, 1.056)	0.044*
Race							
White	2255	2271	28.2	31.5	0.863	(0.776, 0.961)	0.010*
Black	182	162	37.4	32.1	1.112	(0.771, 1.605)	0.302
Oriental/other	74	66	27.0	51.5	0.497	(0.268, 0.920)	0.003*
Countries							
Non US	1418	1414	26.3	30.1	0.844	(0.734, 0.969)	0.014*
US	1093	1085	32.0	34.6	0.905	(0.782, 1.048)	0.228
Etiology of HF							
Ischemic	1446	1419	32.6	33.5	0.959	(0.844, 1.089)	0.474
Nonischemic	1065	1080	23.7	30.1	0.749	(0.635, 0.883)	0.0008*
NYHA							
I/II	1562	1538	22.4	24.6	0.901	(0.779, 1.042)	0.192
III	907	906	38.3	42.7	0.844	(0.730, 0.976)	0.023*
IV	42	55	61.9	65.5	0.842	(0.495, 1.432)	0.424
LVEF							
Below median	1211	1174	33.0	38.2	0.826	(0.722, 0.946)	0.006*
At or above median	1298	1325	24.9	26.6	0.927	(0.797, 1.078)	0.297
Norepinephrine							
Below median	1071	1079	23.9	27.1	0.885	(0.748, 1.047)	0.109
At or above median	1070	1081	35.0	36.0	0.932	(0.809, 1.075)	0.418

ACEI=angiotensin converting enzyme inhibitor; BB=beta blocker; BL=baseline

CI=confidence interval; LVEF=left ventricular ejection fraction; NYHA=New York Heart Association

Plc=placebo; Val=valsartan

*Indicates statistically significantly different from placebo, p<0.05

Table 3-15. Morbidity in subgroups: baseline background HF therapy, Study 107

Subgroup	N		Morbidity, %		Hazard ratio	(95% CI)	p-value
	Val n=2511	Plc n=2499	Val	Plc			
ACEI Use							
No ACEI	185	181	24.9	42.5	0.560	(0.385, 0.813)	0.0002*
ACEI	2326	2318	29.1	31.2	0.901	(0.812, 1.001)	0.096
Beta Blocker Use							
No beta blocker	1644	1616	30.8	37.1	0.794	(0.705, 0.894)	0.0001*
Beta blocker	867	883	25.0	22.9	1.112	(0.917, 1.347)	0.343
ACEI/Beta Blocker Use							
BB=no/ACEI=no	112	114	27.7	47.4	0.561	(0.357, 0.879)	0.003*
BB=no/ACEI=yes	1532	1502	31.0	36.3	0.817	(0.722, 0.924)	0.002*
BB=yes/ACEI=no	73	67	20.5	34.3	0.578	(0.294, 1.137)	0.037*
BB=yes/ACEI=yes	794	816	25.4	21.9	1.185	(0.969, 1.450)	0.104
BB or ACEI or neither	1717	1683	30.3	37.0	0.785	(0.698, 0.882)	0.00003*

HF=heart failure; ACEI=angiotensin converting enzyme inhibitor; BB=beta blocker

CI=confidence interval; Plc=placebo; Val=valsartan

*Indicates statistically significantly different from placebo at the level of 0.05, $p < 0.05$

There was generally no influence of age, gender, race, region, HF etiology, baseline NYHA class, baseline LVEF or baseline neurohormones on mortality. Some of these subgroups contained small sample sizes and, therefore, results should be interpreted cautiously. In patients not receiving an ACEI at baseline, there was a significant reduction in mortality with valsartan compared to placebo, although the number of patients in this subgroup was relatively small (approximately 7% of patients). Conversely, in patients receiving a beta-blocker, the effect on mortality unexpectedly favored placebo with the effect being limited to those patients receiving both a beta-blocker and an ACEI. Patients receiving a beta-blocker without an ACEI, or an ACEI without a beta-blocker had observed mortality rates in the valsartan group which were slightly lower than in the placebo group but the differences were not statistically significant. When evaluating the subgroup of patients receiving either a beta-blocker alone, an ACEI alone, or neither, the valsartan group demonstrated a slightly lower mortality rate than in the placebo group, but the difference was not statistically significant.

The beneficial effect of valsartan on morbidity was generally consistent across patient subgroups including age, gender, race, region, HF etiology, baseline NYHA class, baseline LVEF, and baseline neurohormones. Some of these subgroups contained small sample sizes and, therefore, results should be interpreted cautiously. Treatment with valsartan generally improved morbidity in the absence or presence of other concomitant HF therapy. In patients not receiving an ACEI, in patients not receiving a beta-blocker, and in patients receiving

neither an ACEI nor a beta-blocker at baseline, there was a significant reduction in risk for time to first morbid event with valsartan compared to placebo. Moreover, patients receiving an ACEI at baseline also demonstrated a trend favoring valsartan. While a benefit was not observed in patients receiving both a beta-blocker and an ACEI, a significantly favorable effect on the morbidity endpoint was demonstrated in valsartan patients receiving either a beta-blocker alone or an ACEI alone. When evaluating the subgroup of patients who were receiving a beta-blocker alone, an ACEI alone, or neither, the valsartan group demonstrated a statistically significant reduction in morbidity compared to the placebo group ($p=0.00003$).

Summary of morbidity and mortality

In Study 107 there were two primary endpoints: time to death and time to first morbid event. Valsartan when combined with existing therapies for chronic heart failure significantly reduced the risk by 13.2% ($p=0.009$) for time to first morbid event, but had a neutral effect on mortality. The beneficial effects of valsartan were particularly noteworthy in reducing the risk for time to first heart failure hospitalization by 27.5% ($p=0.00001$).

Most of the subgroups based on demographic or baseline evaluations responded similarly to the whole study population. It was noted that the small subgroup of patients not treated with an ACE inhibitor had a notable reduction in mortality and morbidity in favor of valsartan. A significant reduction in morbidity in favor of valsartan was noted in patients not treated with beta-blocker. Moreover, a significant reduction in morbidity was also demonstrated in patients receiving either a beta-blocker alone or ACE inhibitor alone. In contrast, the effects on mortality and morbidity favored placebo in patients receiving both an ACE inhibitor and a beta-blocker. The results tend to imply that the favorable effect of valsartan may be most prominent in patients not treated with two neurohormonal inhibitors and that the combination of all three agents may not confer any additional benefits. However, this unexpected subgroup analysis result must be interpreted cautiously as it is not known whether these represent true differences or chance effects.

3.2.4. Secondary Endpoint Results

The secondary variables included changes from baseline in NYHA functional class, signs and symptoms of CHF, quality-of-life scores, LV internal diastolic diameter, ejection fraction, and neurohormonal levels.

NYHA Class and Signs and Symptoms of CHF

Table 3-16 presents the results for the signs and symptoms and NYHA class at endpoint for Study 107.

Table 3-16. Number (%) of patients with signs and symptoms of HF and NYHA Class in studies with treatment duration ≥ 12 weeks, at endpoint, Study 107

Variable	Treatment group	N	Improvement N (%)	Deterioration N (%)
NYHA Class	Valsartan	2494	575 (23.1) ‡	252 (10.1)
	Placebo	2484	513 (20.7)	319 (12.8)
Jugular venous distension	Valsartan	2494	199 (8.0) ‡	137 (5.5)
	Placebo	2482	188 (7.6)	179 (7.2)
Edema	Valsartan	2494	294 (11.8) †	253 (10.1)
	Placebo	2482	240 (9.7)	305 (12.3)
Rales	Valsartan	2494	176 (7.1) ‡	152 (6.1)
	Placebo	2482	159 (6.4)	206 (8.3)
Third heart sound	Valsartan	2494	332 (13.3)	139 (5.6)
	Placebo	2482	296 (11.9)	139 (5.6)
Paroxysmal nocturnal dyspnea	Valsartan	2494	164 (6.6) †	121 (4.9)
	Placebo	2483	142 (5.7)	173 (7.0)
Dyspnea at rest	Valsartan	2494	108 (4.3)*	159 (6.4)
	Placebo	2483	89 (3.6)	183 (7.4)
Dyspnea on effort	Valsartan	2494	853 (34.2) †	470 (18.8)
	Placebo	2483	785 (31.6)	528 (21.3)
Fatigue	Valsartan	2494	790 (31.7) †	539 (21.6)
	Placebo	2483	730 (29.4)	628 (25.3)
Orthopnea	Valsartan	2494	353 (14.2)	265 (10.6)
	Placebo	2483	342 (13.8)	286 (11.5)

*Indicates statistically significantly different from placebo, $p < 0.05$

†Indicates statistically significantly different from placebo, $p < 0.01$

‡Indicates statistically significantly different from placebo, $p < 0.001$

Valsartan demonstrated improvements in NYHA Class and individual signs and symptoms of HF in patients with NYHA Class II-IV HF already receiving standard HF therapy in the long-term Study 107.

Quality of Life Scores

Tables 3-17 and 3-18 and Figures 3-6 and 3-7 present the baseline values and change from baseline in overall Minnesota Living with Heart Failure Questionnaire (LHFQ) score in study 107. A decrease in Minnesota LHFQ score is defined as an improvement in quality of life.

Table 3-17. Mean baseline values and mean change from baseline in overall score in Minnesota Living with Heart Failure questionnaire at endpoint, Study 107

Study	Treatment group	N	Mean BL (SD)	LSM change (SE)	LSM treatment difference (SE)	(95% CI) p-value
107	Valsartan	1504	32.6 (23.1)	0.19 (0.47)	-1.75 (0.62)	(-2.97,-0.53) 0.005*
	Placebo	1506	31.8 (22.8)	1.94 (0.48)		

BL=baseline; SD=standard deviation; SE=standard error

LSM=least squares mean; CI=confidence interval

*Indicates statistical significance at level of 0.05 ($p < 0.05$)

Figure 3-6. Mean change from baseline in Minnesota LHFQ overall score by month, Study 107

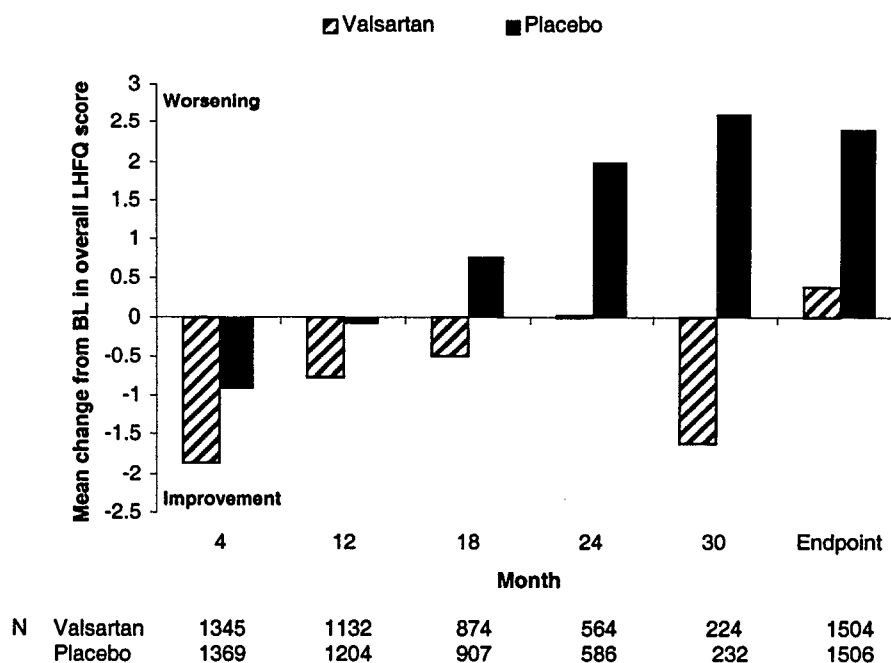


Figure 3-7. Mean change from baseline in overall score of LHFQ by subgroup at endpoint, study 107

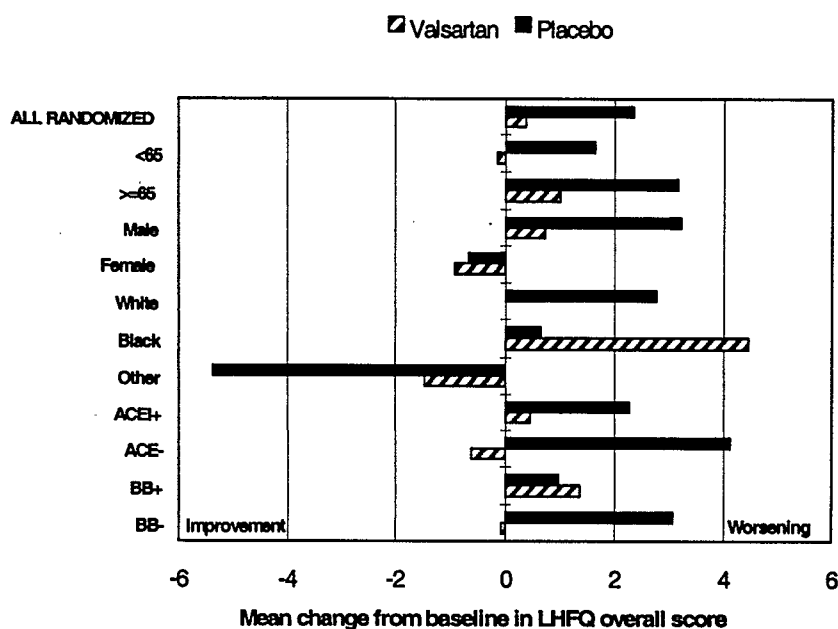


Table 3-18. Mean baseline values and mean change from baseline in emotional and physical scores in Minnesota Living with Heart Failure questionnaire at endpoint, Study 107

Score	Treatment group	N	Mean BL (SD)	LSM change	LSM treatment difference (SE)	(95% CI) p-value
Emotional	Valsartan	1501	6.7 (6.6)	-0.15	-0.39 (0.18)	(-0.74,-0.03) 0.032*
	Placebo	1506	6.8 (6.6)	0.24		
Physical	Valsartan	1503	14.8 (10.6)	0.16	-0.76 (0.29)	(-1.33,-0.18) 0.010*
	Placebo	1505	14.2 (10.4)	0.92		

BL=baseline; SE=standard error

LSM=least squares mean; CI=confidence interval

*Indicates statistical significance at level of 0.05 (p<0.05)

In Study 107, patients in the valsartan group showed little change in overall LHFQ score from baseline to endpoint while there was a worsening in the placebo group. The difference was statistically significant.

Summary of Quality-of-Life Scores

Valsartan added to patients' standard therapy for HF has significant beneficial effects on quality of life compared to placebo. The benefits of valsartan on maintaining quality of life was consistently demonstrated at all timepoints during study 107 with consistent effects on both subscores of the Minnesota LHFQ.

Left ventricular ejection fraction

Left ventricular ejection fraction was measured by echocardiography in Study 107. Post-treatment LVEF was measured at months 4 and 12, every 6 months thereafter, and at study endpoint if the patient terminated study medication permanently.

Tables 3-19 and 3-20 present the baseline and mean changes from baseline in LVEF in study 107. Figures 3-8 and 3-9 presents the mean change from baseline in LVEF by month in Study 107.

Table 3-19. Mean baseline left ventricular ejection fraction (%), Study 107¶

Study	Treatment group	N	Mean BL (SD)
107	Valsartan	2509	26.6 (7.3)
	Placebo	2499	26.9 (7.0)

BL=baseline; SD=standard deviation; d=days

¶Includes all randomized patients with a baseline value but not necessarily with respective post-baseline or endpoint value

Table 3-20. Mean change from baseline in left ventricular ejection fraction (%) at endpoint, Study 107

Study	Treatment group	N	LSM Change	Difference from placebo	(95% CI) p-value
107	Valsartan	2300	4.01	0.83	(0.35,1.31) 0.001*
	Placebo	2336	3.18		

LSM =Least squares mean CI=confidence interval

* Indicates statistically significantly different from placebo at the level of 0.050 (p<0.05)

Figure 3-8. Mean change from baseline in left ventricular ejection fraction (%) by month, Study 107

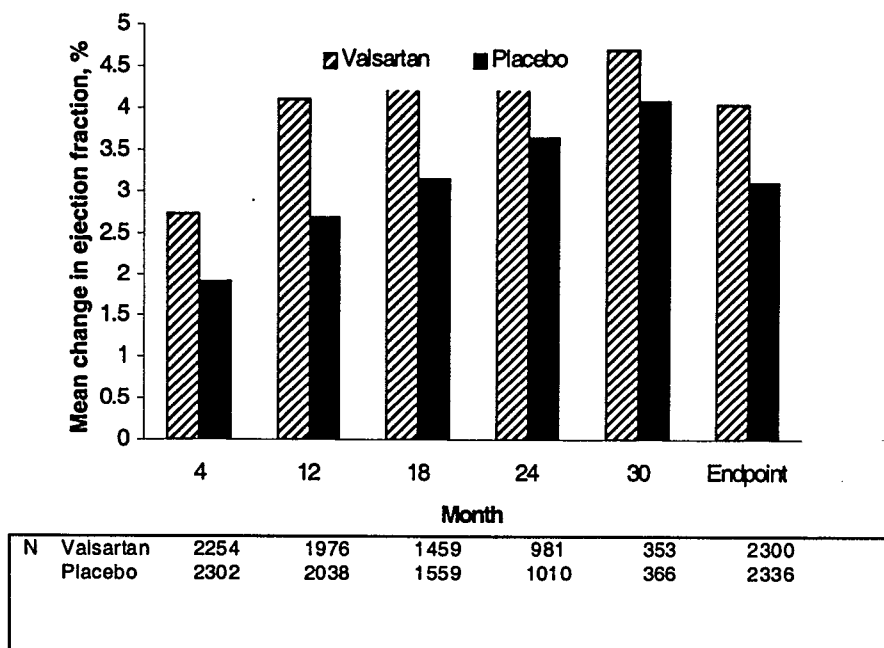
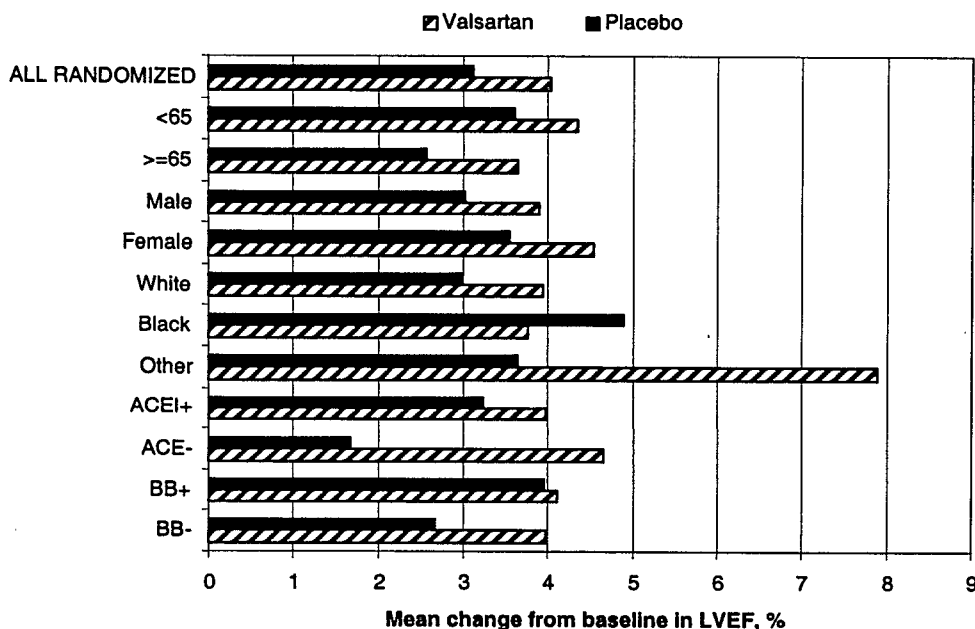


Figure 3-9. Mean change from baseline in ejection fraction (%) at endpoint by subgroup, study 107



In Study 107, clinically and statistically significant improvements were observed at endpoint.

Summary of left ventricular function

Valsartan produced statistically significant improvements in LVEF compared to placebo, occurring as early as 4 months after treatment and persisting for the duration of valsartan treatment in the long-term trial 107, approximately 21 months.

Left ventricular volume

In Study 107, patients were required to have a baseline left ventricular internal diastolic diameter (LVIDD) >2.9 cm/m². In Study 107, echocardiography was done at months 4 and 12, every 6 months thereafter, and at study endpoint (24-36 months). Table 3-21 presents the mean baseline values and change from baseline in LVIDD in Study 107. Figure 3-10 presents mean changes from baseline in LVIDD by month in Study 107.

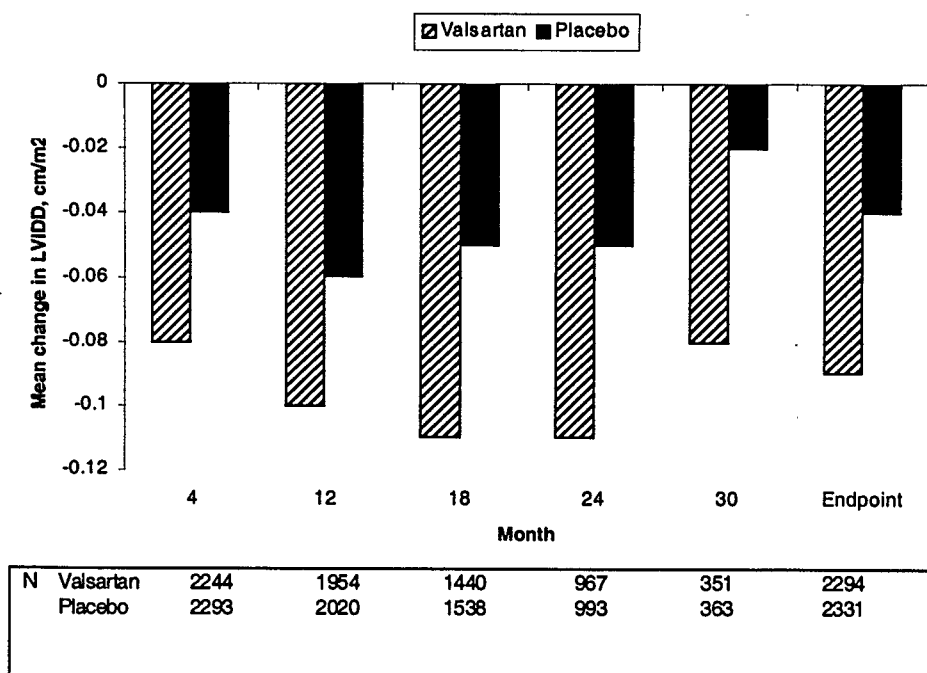
Table 3-21. Mean baseline values and mean change from baseline in left ventricular end-diastolic internal diameter adjusted by body surface area (LVIDD/BSA, cm/m²) at endpoint, Study 107

Study	Treatment group	N	Mean BL (SD)	LSM change (SE)	LSM treatment difference (SE)	(95% CI) p-value
107	Valsartan	2294	3.64 (0.52)	-0.08 (0.01)	-0.05 (0.01)	(-0.07,-0.03) <0.001*
	Placebo	2331	3.65 (0.53)	-0.03 (0.01)		

BL=baseline; SD=standard deviation; SE=standard error; BSA=body surface area
LSM=Least squares mean; CI=confidence interval

*Indicates statistically significantly different from placebo at level of 0.05 (p<0.05)

Figure 3-10. Mean change from baseline in left ventricular end-diastolic internal diameter (LVIDD) by month, Study 107



Valsartan produced statistically significant improvements at endpoint in left ventricular volume, as measured by echocardiographic LVIDD compared to placebo in Study 107. Improvement in LVIDD was seen at all assessed timepoints in Study 107.

Chronic Effects (neurohormone levels)

Tables 3-22, 3-23, and 3-24 present the baseline neurohormone values and change from baseline in plasma norepinephrine and brain natriuretic peptide (BNP) in Study 107. Figures 3-11, 3-12, 3-13, and 3-14 present the mean change in plasma norepinephrine and the mean change in plasma BNP from baseline by month.

Table 3-22. Mean baseline neurohormone values¶, Study 107

Neurohormone	Valsartan		Placebo	
	N	Mean (SD)	N	Mean (SD)
PRA, ng/mL/h	2141	14.6 (23.8)	2150	14.0 (23.6)
Aldosterone, pg/mL	2114	131.5 (118.0)	2126	140.1 (136.7)
Norepinephrine, pg/mL	2141	455.6 (270.2)	2160	472.0 (368.2)
Endothelin I, fmol/mL (US)	964	2.0 (1.7)	970	1.9 (1.6)
Big endothelin, fmol/mL (nonUS)	1180	1.0 (0.7)	1179	1.0 (0.6)
Brain natriuretic peptide, pg/mL	2145	183.5 (230.7)	2160	177.6 (229.6)

SD=standard deviation

¶Includes all randomized patients with a baseline value but not necessarily with respective post-baseline or endpoint value

Table 3-23. Mean change from baseline in plasma norepinephrine (pg/mL) at endpoint, Study 107

Treatment group	N	LSM change (SE)	LSM treatment difference (SE)	(95% CI)	p-value
Valsartan	1941	11.91 (6.08)	-28.9 (8.0)	(-44.5,-13.0)	<0.001*
Placebo	1979	40.79 (6.09)			

LSM=least squares mean

*Indicates statistically significantly different from placebo at level of 0.05 (p<0.05)

Figure 3-11. Mean change from baseline in plasma norepinephrine by month (pg/mL), Study 107

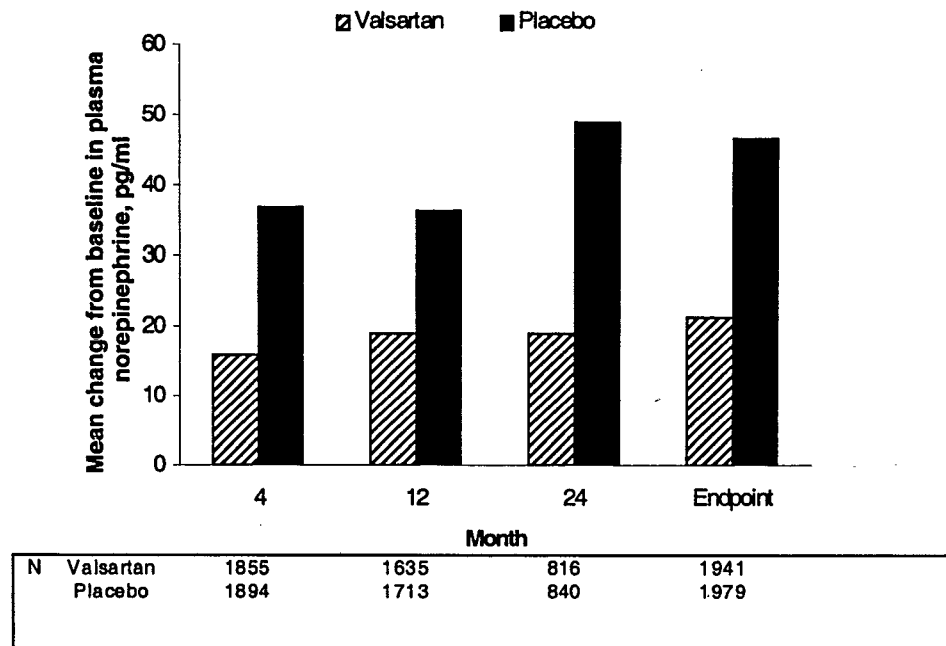


Figure 3-12. Change from baseline in plasma norepinephrine (pg/mL) at endpoint in various subgroups, study 107

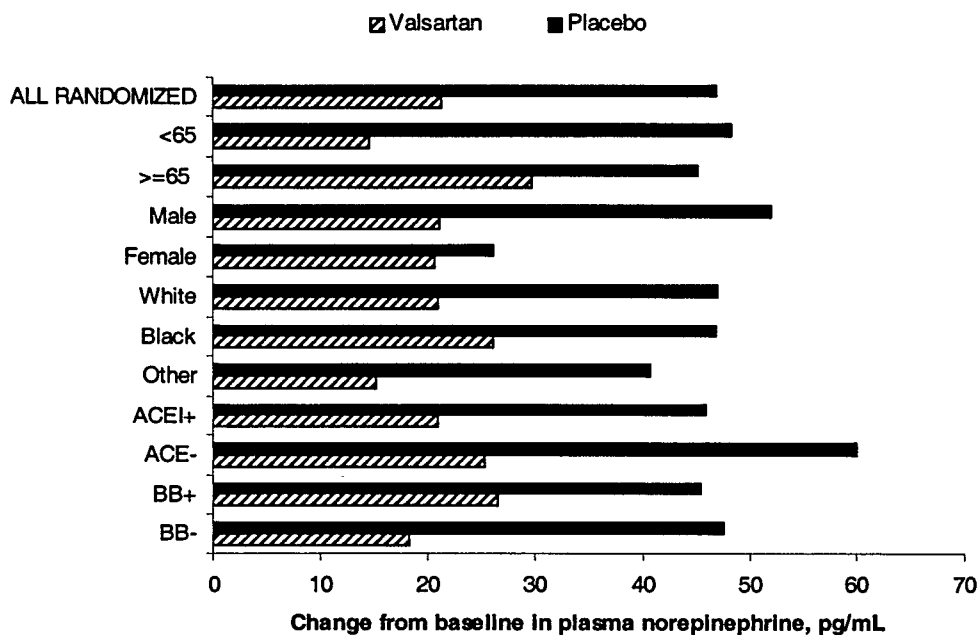


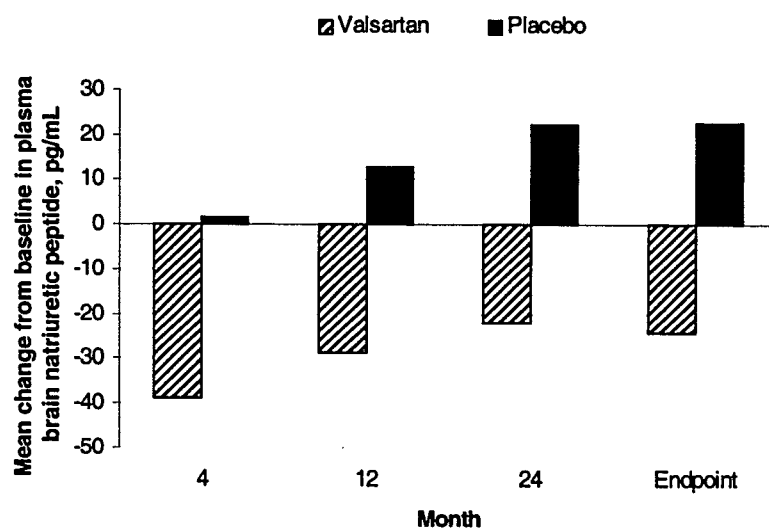
Table 3-24. Mean change from baseline in plasma brain natriuretic peptide at endpoint, Study 107

Treatment group	N	LSM change (SE)	LSM treatment difference	(95% CI)	p-value
Valsartan	1940	-20.8 (4.9)	-43.8	(-56.5,-31.0)	<0.001*
Placebo	1979	23.0 (4.9)			

LSM=least squares mean

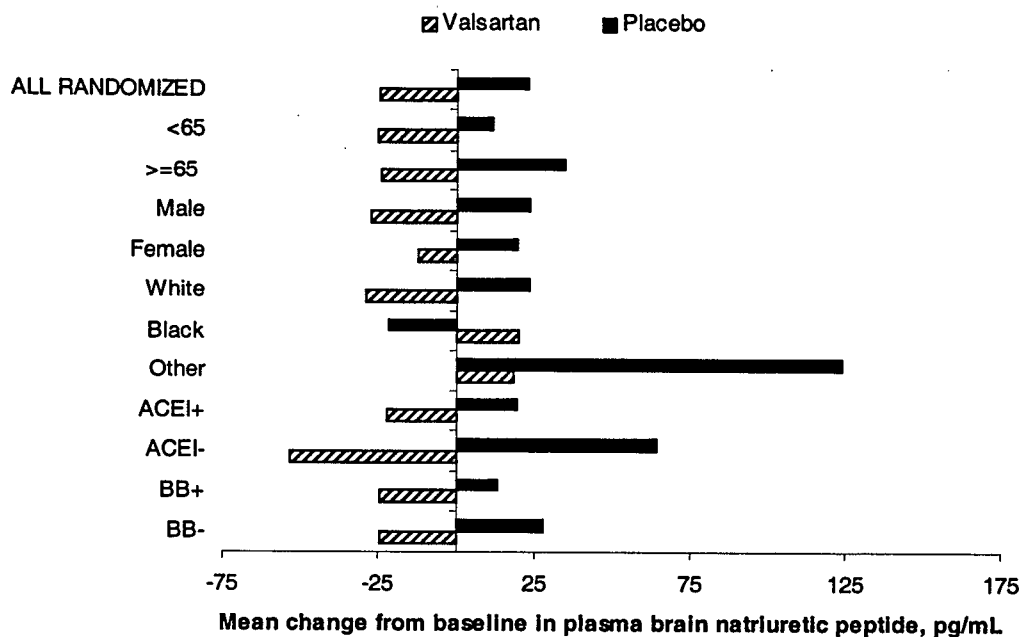
*Indicates statistically significantly different from placebo at level of 0.05 (p<0.05)

Figure 3-13. Mean change from baseline in plasma brain natriuretic peptide (pg/mL) by month, Study 107.



N	Valsartan	1850	1633	823	1940
	Placebo	1890	1710	844	1979

Figure 3-14. Change from baseline in plasma brain natriuretic peptide (pg/mL) at endpoint in various subgroups, study 107



Both treatment groups had increases in plasma norepinephrine over the course of the study; however, valsartan-treated patients had lesser increases at months 4, 12, 24, and at endpoint, with statistically significant differences ($p < 0.05$) from placebo at the three time points at which statistical tests were performed, 4 months, 12 months, and endpoint. In all subgroups examined, placebo-treated patients had greater increases in plasma norepinephrine at endpoint than valsartan-treated patients.

Valsartan-treated patients had decreases in plasma brain natriuretic peptide, starting at 4 months and persisting for the duration of study. In contrast, placebo-treated patients had increases in BNP. These treatment differences were statistically significant ($p < 0.05$) from placebo at the three time points at which statistical tests were performed, 4 months, 12 months, and endpoint. In all subgroups examined with the exception of the two small racial subgroups (blacks and "others"), placebo-treated patients had increases in BNP and valsartan-treated patients had decreases in BNP. These subgroup analyses should be interpreted cautiously.

3.3. Studies 106,107/Sub-study 02, and 110

3.3.1. Study Designs

Study 106 was a placebo-controlled trial to assess the effect of valsartan on exercise capacity, quality of life, LVEF and NYHA classification, and signs and symptoms of CHF in patients with stable chronic congestive heart failure. The study included patients with resting LVEF $\leq 40\%$ on multiple gated acquisition radionuclide angiography (MUGA) within two weeks of entry into the study. Patients were required to have remained at a stable dosage regimen of their HF medication (diuretics, ACE inhibitors, digoxin, vasodilators, and beta blockers) and/or background therapy with alpha-adrenergic blockers and calcium channel blockers at least one week prior to their baseline qualifying MUGA through the randomization visit. Patients were excluded who had taken angiotensin II antagonists or chronic intravenous inotropes or intravenous vasodilator therapy within 3 months of entry into the study or required these medications during the study. Patients with any arrhythmia or other condition which would contraindicate or limit the patient's ability to perform exercise testing or result in an exercise endpoint other than dyspnea or fatigue related to HF were excluded. Eligible patients entered a 1 to 3 week washout period during which the patient's cardiovascular status was to be stabilized. Exercise capacity stabilization was then determined over two to three exercise tests during the 1 to 2 week placebo run-in period. Patients were required to exercise for range of duration time on a maximal exercise protocol for each required exercise test (2 or 3 tests) based on their age at entry and have two consecutive tests with a duration of exercise within 25% of each other, with each test having an endpoint of either fatigue or shortness of breath. Eligible patients were randomized to receive either valsartan 40 mg BID, valsartan 80 mg BID, valsartan 160 mg BID or placebo, which was administered for 16 weeks; randomization was stratified by use of ACE inhibitor therapy. Patients randomized to valsartan 160 mg BID received 80 mg BID for one week then 160 mg BID for the remainder of the double blind treatment period. Exercise tolerance testing was done periodically during the double-blind treatment period. A total of 905 patients were enrolled in the trial; 770 patients were randomized and 650 patients completed the trial. A total of 709 patients were included in the primary efficacy analysis of change from baseline in mean exercise tolerance time (ETT) using a modified Naughton protocol and 690 patients were included in the primary efficacy analysis of change from baseline in overall Minnesota Living with Heart Failure Questionnaire (LHFQ) score.

Study 107/Sub-study 02 was a placebo-controlled sub-study that assessed the effect of twice-a-day administration of valsartan compared to placebo on exercise capacity as measured by the distance walked in a six-minute walk test in patients with stable, chronic CHF, 4 months following randomization into valsartan study 107. This sub-study had the same trial design, dosing interval, inclusion and exclusion criteria, controls, and blinding as study 107.

Study 110 was an active controlled study to assess the efficacy and safety of valsartan compared to enalapril on exercise capacity (six minute walk test), LVEF, dyspnea fatigue

index, and quality of life in patients with stable moderate chronic heart failure. This study included patients with resting LVEF $\leq 45\%$ (measured by echocardiography) and exercise not limited by any disease other than HF. Patients were required to have received an ACE inhibitor for 3 months prior to study entry, remained on a stable dosage of HF medication and had stable clinical status for 2 weeks prior to entry into the study and during the run-in period. Patients were excluded who had taken angiotensin receptor blockers in the 3 months prior to entry into the study or who had limited ability to exercise for any reason other than HF. Eligible patients entered a 2-week single-blind placebo run-in period, during which they remained on open ACE inhibitor treatment and study qualification procedures were performed. Patients meeting the criteria for randomization were randomized to valsartan or enalapril for 12 weeks. Dosage was increased after 1 week, from 80 mg once daily to 160 mg once daily for valsartan, and 5 mg BID to 10 mg BID for enalapril. Exercise capacity was measured periodically during the 12-week treatment period. A total of 146 patients were enrolled in the trial; 141 patients were randomized and 127 patients completed the trial. A total of 134 patients were included in the primary efficacy analysis of exercise capacity as assessed by the six minute walk test.

3.3.2. Efficacy results

Exercise capacity

Maximal exercise testing

In Study 106, maximal exercise testing was done using a modified Naughton protocol. Criteria for randomization were two consecutive exercise tests within 25% of each other and within the following durations according to the age of the patient: age 18-29 years: 3-14 minutes; age 30-50 years: 3-12 minutes; >50 years: 3-10 minutes. The exercise tolerance test was repeated at weeks 8, 12, and 16 of the 16-week treatment period. The endpoint tests results for exercise tolerance time (ETT) in Study 106 are presented in Table 3-25 (with 0 assigned for death or inability to walk DUE TO HF) and Table 3-26 (with 0 assigned for death or inability to walk DUE TO ANY REASON).

Table 3-25. Mean change from baseline in exercise duration (seconds) as assessed by maximal exercise testing, at endpoint, with 0 assigned for death or inability to walk "due to HF", Study 106

	Valsartan 40 mg BID	Valsartan 80 mg BID	Valsartan 160 mg BID	Placebo
N	168	180	182	179
BL mean (SD)	438.8 (138.2)	430.0 (142.8)	430.8 (141.4)	434.5 (132.2)
Least squares mean change from baseline, sec	85.1	85.4	68.6	65.7
LS mean difference (SE) from placebo	19.4 (16.1)	19.7 (15.8)	2.9 (15.7)	
95% CI for LS mean difference from placebo	(-12.3, 51.0)	(-11.3, 50.7)	(-28.0, 33.8)	
p-value disregarding multiple comparisons	0.2296	0.2119	0.8530	
p-value adjusted for multiple comparisons	0.4846	0.4536	0.9955	

LS=least squares; SE=standard error of LS mean difference; CI=confidence interval

ITT=intent-to-treat population, patients with values at baseline and endpoint

Table 3-26. Mean change from baseline in exercise duration (seconds) as assessed by maximal exercise testing, at endpoint, with 0 assigned for death or inability to walk "due to any reason", Study 106

	Valsartan 40 mg BID	Valsartan 80 mg BID	Valsartan 160 mg BID	Placebo
N	171	181	187	185
BL mean (SD)	436.3 (138.4)	428.8 (143.4)	427.8 (143.4)	437.0 (131.7)
Least squares mean change from baseline, sec	68.3	80.6	48.5	38.8
LS mean difference (SE) from placebo	29.5 (18.4)	41.7 (18.1)	9.6 (17.9)	
95% CI for LS mean difference from placebo	(-6.6, 65.5)	(6.3, 77.2)	(-25.5, 44.8)	
p-value disregarding multiple comparisons	0.109	0.021	0.591	
p-value adjusted for multiple comparisons	0.256	0.056	0.909	

LS=least squares; SE=standard error of LS mean difference; CI=confidence interval
ITT=intent-to-treat population, patients with values at baseline and endpoint

Table 3-27 presents the summary statistics for subgroup analyses by ACE inhibitor use for change from baseline in ETT.

Table 3-27. Subgroup analyses of exercise tolerance time (ETT): mean changes from baseline in exercise duration (seconds) at endpoint, with 0 assigned for patients unable to walk due to HF or death, Study 106

	Val 40 mg BID			Val 80 mg BID			Val 160 mg BID			Placebo		
	N	BL s	Chg s	N	BL s	Chg s	N	BL s	Chg s	N	BL s	Chg s
ACEI Use												
Yes	149	439	74	156	426	73.8	154	433	57	154	444	64.7
No	19	441	158	24	456	126	28	418	125	25	412	58.4

BL=baseline; Chg=change; s=seconds

ACEI=angiotensin converting enzyme inhibitor; Val=valsartan

Six-minute walk test

The six-minute walk test was done in Study 110, at weeks 6 and 12 of the 12 week treatment period, and a substudy of 107, at weeks 8 and 17 of the 24-36 month treatment period. Table 3-28 presents the change from baseline in exercise tolerance test time in Study 110.

Table 3-28. Mean change from baseline in exercise capacity (meters) as assessed by the 6-minute walk test at endpoint, Study 110

Treatment group	N ^a	BL mean (SD)	LSM change (SE)	LSM treatment difference (95% CI)	p-value ^b	p-value ^c
Valsartan	67	421.7 (113.3)	3.01 (8.54)	1.12 (-21.89 to 24.12)	<0.001*	0.462
Enalapril	67	426.0 (114.4)	1.90 (8.51)			

BL=baseline; LSM=Least squares mean; CI=confidence interval; SD=standard deviation; SE=standard error

^a 0 assigned for patients unable to walk due to death or HF

^b one-sided p-value for test for non-inferiority

^c one-sided p-value for test for superiority

* indicates statistical significance at the one-sided 0.025 level

Table 3-29 presents the change from baseline in the six-minute walk test at baseline in the substudy of Study 107.

Table 3-29. Baseline mean and mean change from baseline in exercise capacity (meters) as assessed by the 6-minute walk test at endpoint, exercise sub-study of Study 107

Treatment group	N	BL mean (SD)	LSM change (SE)	LSM treatment difference (95% CI)	p-value
Valsartan	320	372.7 (110.2)	14.91 (4.61)	1.18 (-11.2, 13.6)	0.852
Placebo	313	373.6 (113.4)	13.73 (4.66)		

BL=baseline; m=meters; LSM=least squares mean; SD=standard deviation;

SE=standard error; CI=confidence interval

Summary of exercise capacity

In Study 106, the addition of valsartan to standard background HF therapy produced greater mean increases from baseline in exercise time on maximal exercise testing compared to placebo; however, no statistically significant improvement over placebo was achieved. Valsartan treated patients not taking ACEI had greater changes from baseline in exercise time than placebo treated patients.

In Study 107/Sub-study 02, both treatment groups demonstrated improvements in exercise capacity, as assessed by the change in distance walked, but there was no statistically significant difference between valsartan and placebo-treated patients.

In Study 110, valsartan was demonstrated to be at least as effective as enalapril in terms of exercise capacity as assessed by the six-minute walk test in patients receiving other standard background HF therapy.

Heart failure signs and symptoms/NYHA Class

In Study 106, for all three valsartan treatment groups, there were higher percentages of valsartan patients who improved and lower percentages of valsartan patients who worsened compared to placebo for NYHA Class at endpoint, although these differences, and the differences for heart failure signs and symptoms, were not statistically significant.

In the active control trial, Study 110, the valsartan and enalapril groups were comparable with respect to number of patients showing improvement in NYHA Class. More patients in the enalapril group than the valsartan group showed improvement in edema (13% vs. 5%). The two treatment groups were otherwise comparable with respect to the number of patients showing improvement in clinical signs of HF. No statistically significant differences between valsartan and enalapril were observed.

Quality of life

Quality of life was assessed using two tools, the Minnesota LHFQ (Study 106 and 110) and the Dyspnea-Fatigue Index (Study 110).

Minnesota LHFQ

Table 3-30 presents the baseline values and change from baseline in overall Minnesota LHFQ score in Study 106 and 110. A decrease in Minnesota LHFQ score is defined as an improvement in quality of life.

Table 3-30. Mean baseline values and mean change from baseline in overall score in Minnesota Living with Heart Failure questionnaire at endpoint, Studies 106 and 110

Study	Treatment group	N	Mean BL (SD)	LSM change (SE)	LSM treatment difference (SE)	(95% CI) p-value
106	Valsartan 40 mg BID	166	37.6 (23.5)	-4.50 (1.11)	-1.24 (1.53)	(-4.25,1.78) 0.7587
	Valsartan 80 mg BID	175	39.9 (24.8)	-3.26 (1.08)	0.00 (1.51)	(-2.97,2.97) >0.9999
	Valsartan 160 mg BID	177	35.1 (22.9)	-3.43 (1.07)	-0.17 (1.51)	(-3.13,2.80) 0.9991
	Placebo	172	39.2 (23)	-3.27 (1.09)		
110	Valsartan	67	21.1 (16.0)	0.66 (1.30)	-0.22 (1.80)	(-3.78,3.35) 0.905
	Enalapril	64	18.2 (12.9)	0.88 (1.33)		

BL=baseline; SD=standard deviation; SE=standard error

LSM=least squares mean; CI=confidence interval

In Study 106, there were slight improvements (reductions in overall LHFQ) seen in all treatment groups although no statistically significant differences between treatment groups were observed. In Study 110, there were no statistically significant difference between valsartan and enalapril.

Dyspnea-Fatigue Index

The Dyspnea-Fatigue Index was performed in Study 110. Table 3-31 presents the mean baseline values and change from baseline for this secondary efficacy variable.

Table 3-31. Mean baseline values and mean change from baseline in Dyspnea-Fatigue Index, at endpoint, Study 110

Treatment group	N	Mean BL (SD)	LSM change (SE)	LSM treatment difference	(95% CI) p-value
Valsartan	67	6.9 (1.6)	-0.24 (0.16)	0.02	(-0.41,0.45) 0.935
Enalapril	64	6.7 (1.6)	-0.26 (0.16)		

SD=standard deviation; BL=baseline; LSM=least squares mean
CI=confidence interval

Small increases in the Dyspnea-Fatigue Index were observed, indicating a slight improvement in symptoms, with no statistically significant differences between the treatment groups.

Summary of quality of life

While there were no statistically significant beneficial effects on quality of life of valsartan added to a patients' standard therapy for HF in trials 106 and 110, the benefits of valsartan on maintaining quality of life was consistently demonstrated at all timepoints during the large long-term study, 107 (mentioned in the quality of life section of section 3.2.3.), with consistent effects on both subscores of the Minnesota LHFQ.

Left ventricular function

Measures of left ventricular function were made in the 16-week exercise Study 106 and the 12-week exercise Study 110.

Left ventricular ejection fraction

Left ventricular ejection fraction was measured by MUGA in Study 106. In Study 106, patients were required to have a baseline LVEF of $\leq 40\%$. Post-treatment LVEF was measured at week 16 of the 16-week treatment period, or at study termination, if the patient discontinued prematurely, in Study 106.

Tables 3-32 and 3-33 present the baseline and mean changes from baseline in LVEF in Study 106.

Table 3-32. Mean baseline left ventricular ejection fraction (%), Study 106 ¶

Study	Treatment group	N	Mean BL (SD)
106	Valsartan 40 mg BID	185	26.4 (7.2)
	Valsartan 80 mg BID	195	27.2 (7.5)
	Valsartan 160 mg BID	198	26.8 (7.5)
	Placebo	191	27.1 (7.3)

BL=baseline; SD=standard deviation; d=days

¶Includes all randomized patients with a baseline value but not necessarily with respective post-baseline or endpoint value

Table 3-33. Mean change from baseline in left ventricular ejection fraction (%) at endpoint, Study 106

Study	Treatment group	N	LSM Change	Difference from placebo	(95% CI) p-value
106	Valsartan 40 mg BID	150	3.02	1.71	(0.05,3.38) 0.0437*
	Valsartan 80 mg BID	168	2.72	1.41	(-0.20,3.01) 0.0856
	Valsartan 160 mg BID	167	3.90	2.59	(0.97,4.20) 0.0017*
	Placebo	169	1.31		

LSM =Least squares mean CI=confidence interval

* Indicates statistically significantly different from placebo at the level of 0.050 (p<0.05)

In Study 106, clinically and statistically significant (p<0.05) results in favor of valsartan 40 mg BID and 160 mg BID over placebo were observed at endpoint.

Atrioventricular plane displacement

Atrioventricular plane displacement, an echocardiographic measurement of left ventricular function was measured in Study 110, at baseline, and at 12 weeks, or at endpoint, in patients who discontinued prematurely. Table 3-34 presents the mean baseline and change from baseline at endpoint in AVPD.

Table 3-34. Mean baseline and mean change from baseline in atrioventricular plane displacement (AVPD, mm) at endpoint, Study 110

Treatment group	N	Mean BL (SD)	LSM change (SE)	LSM treatment difference (SE)
Valsartan	67	8.73 (2.27)	0.32 (0.16)	0.02 (0.22)
Enalapril	64	8.77 (2.17)	0.30 (0.16)	

BL= baseline; SD= standard deviation; LSM= least squares mean; SE= standard error
CI= confidence interval

There was a non-significant improvement in atrioventricular plane displacement in both treatment groups.

Summary of left ventricular function

Valsartan produced statistically significant improvements in LVEF compared to placebo, occurring as early as 4 months after treatment, as seen in Study 106. No significant treatment difference between valsartan and enalapril was observed in Study 110.

Left ventricular volume

Left ventricular volume was assessed by measurement of the LVIDD in Study 110. In Study 110, echocardiography was done at baseline and at week 12, or at endpoint in patients who discontinued prematurely. Table 3-35 presents the mean baseline values and change from baseline in LVIDD in Study 110.

Table 3-35. Mean baseline values and mean change from baseline in left ventricular end-diastolic internal diameter adjusted by body surface area (LVIDD/BSA, cm/m²) at endpoint, Study 110

Study	Treatment group	N	Mean BL (SD)	LSM change (SE)	LSM treatment difference (SE)	(95% CI) p-value
110	Valsartan	67	3.57 (1.18)	-0.41 (0.10)	-0.22 (0.13)	(-0.49, 0.04) 0.098
	Enalapril	63	3.70 (1.17)	-0.18 (0.10)		

BL=baseline; SD=standard deviation; SE=standard error; BSA=body surface area
LSM=Least squares mean; CI=confidence interval

In Study 110, a positive trend in favor of valsartan versus enalapril was observed.

3.4. Summary and Conclusions of Well-Controlled Studies

Morbidity and mortality

In Study 107 there were two primary endpoints: time to death and time to first morbid event. Valsartan when combined with existing therapies for chronic heart failure significantly reduced the risk by 13.2% ($p = 0.009$) for time to first morbid event, but had a neutral effect on mortality. The beneficial effects of valsartan were particularly noteworthy in reducing the risk for time to first heart failure hospitalization by 27.5% ($p = 0.00001$).

Most of the subgroups based on demographic or baseline evaluations responded similarly to the whole study population. It was noted that the small subgroup of patients not treated with an ACE inhibitor had a significant reduction in mortality and morbidity in favor of valsartan. A significant reduction in morbidity in favor of valsartan was noted in patients not treated with beta-blocker. Moreover, a significant reduction in morbidity was also observed in valsartan patients receiving either a beta-blocker alone or ACE inhibitor alone. In contrast, the effects on mortality and morbidity favored placebo in patients receiving both an ACE inhibitor and a beta-blocker. The results tend to imply that the favorable effect of valsartan may be most prominent in patients not treated with two neurohormonal inhibitors and that the combination of all three agents may not confer any additional benefits. This unexpected subgroup analysis result must be interpreted cautiously as it is not known whether these represent true differences or chance effects.

Exercise capacity

In Study 106, the addition of valsartan to standard background HF therapy produced greater mean increases from baseline in exercise time on maximal exercise testing compared to placebo; however, no statistically significant improvement over placebo was achieved. Valsartan treated patients not taking ACE inhibitors had greater changes from baseline in exercise time than placebo treated patients.

In the exercise sub-study of Study 107, both treatment groups demonstrated improvements in exercise capacity, as assessed by the change in distance walked, but there was no statistically significant difference between valsartan and placebo-treated patients.

In Study 110, valsartan was demonstrated to be at least as effective as enalapril in terms of exercise capacity as assessed by the six-minute walk test in patients receiving other standard background HF therapy.

Hemodynamics

Acute and chronic (after 4 weeks) central and peripheral hemodynamic effects were observed after dosing with valsartan, given with or without chronic therapy with an ACE inhibitor. In general, a greater vasodilatory effect was observed on Day 0 than after chronic dosing. In Study 104, valsartan 160 mg BID in addition to chronic ACE inhibitor therapy produced

sustained hemodynamic effects after four weeks of dosing. The data from Study 104 suggests that the hemodynamic effects are greater with the 160 mg BID dose than lower doses.

Heart failure signs and symptoms/NYHA Class

Valsartan demonstrated improvements in NYHA Class and individual signs and symptoms of HF in patients with NYHA Class II-IV HF already receiving standard HF therapy, particularly in the long term Study 107.

Quality of life

Valsartan added to patients' standard therapy for HF has significant beneficial effects on quality of life compared to placebo. While this observation was not statistically significant in all trials, the benefits of valsartan on maintaining quality of life was consistently demonstrated at all timepoints during the large long-term study, 107, with consistent effects on both subscores of the Minnesota LHFQ. In the active-controlled trial, study 110, valsartan showed comparable effects to enalapril on quality of life.

Left ventricular function

Valsartan produced statistically significant improvements in LVEF compared to placebo, occurring as early as 4 months after treatment, as seen in Studies 106 and 107, and persisting for the duration of valsartan treatment in the long term trial 107, approximately 21 months.

Left ventricular volume

Valsartan produced statistically significant improvements in left ventricular volume, as measured by echocardiographic LVDD compared to placebo in Study 107.

Neurohormones

Valsartan produced increases in plasma renin activity and decreases in plasma aldosterone, norepinephrine, and atrial peptide after 28 days of dosing, although the differences from placebo failed to reach statistical significance at many time points. In Study 104, the treatment effects of valsartan 160 mg BID were greater than that of valsartan 80 mg BID for plasma norepinephrine and aldosterone, suggesting a dose response in pharmacologic activity.

Starting at 4 months of treatment and persisting for the duration of the long-term morbidity and mortality Study 107, valsartan produced statistically significant effects on plasma norepinephrine and plasma brain natriuretic peptide that were consistent among the subgroups.

3.5. Long term efficacy information

The benefits of valsartan, as demonstrated by the positive results of multiple endpoints in Study 107 and described in Section 3.2, support the long-term efficacy of valsartan.

4. Overall safety summary

A total of 5 completed studies are presented in this Briefing Summary. It is focussed primarily on the data obtained from these 5 adequate and well controlled studies (as of October 1st, 2000) designed to evaluate safety and efficacy in patients with HF NYHA Class II- IV (Table 4-1). This includes one long-term study to evaluate morbidity and mortality.

The main focus of the safety analysis is on the completed trials which provide comprehensive adverse experience data and clinical laboratory data. Safety-analyzable patients from the completed trials were grouped into four different datasets, depending on the types of the trials:

- Pooled data from double-blind controlled short-term trials: 103, 104, 106, 107 (first 4 months' treatment), and 110. The treatment durations of these trials ranged from one to four months. This is the largest dataset of controlled trials. The first 7 visits (approximately 4 months) of Study 107 was chosen to be consistent with the maximum treatment duration of the other trials in this dataset; further, it was expected that most adverse events that were potentially related to trial drug would likely be seen during this period. **This is considered the primary dataset and will be referred to as such throughout the text.**
- Pooled data from double-blind placebo-controlled short-term trials described above, but without positive-controlled Study 110 [ie 103, 104, 106, 107 (first 4 months treatment)]. Limited data displays are included. **This is considered dataset B and will be referred to as such throughout the text.**
- Double-blind placebo-controlled long-term trial: 107 (dataset C).

Data for the valsartan-treated patients are displayed by total daily dose (ie 0 mg, 80 mg, 160 mg and 320 mg/day) as well as for all valsartan-treated patients (ie all doses combined). Patients may be counted in more than one valsartan dose group, but only once in the "all" column/row. In Study 106, patients randomized to the valsartan 160 mg BID group (320 mg/day) received valsartan 80 mg BID (160 mg/day) for one week and then were to be titrated to the higher dose. Therefore, for this study, the 160 mg total daily dose column for valsartan includes patients randomized to receive this dose, as well as patients randomized to receive 320 mg daily. In Study 107, the valsartan treatment interruptions during the double-blind period are captured in the "0 mg" column and included in the "all" column except in the exposure tables. No other pooled trials captured drug interruptions.

4.1. Studies used to assess safety

Summaries of completed double-blind studies are presented in Table 4-1.

Table 4-1. Summary of completed double-blind studies used for integrated safety evaluation

Study No.	Phase	Control	Treatment exposure	No. of randomized patients per treatment group		Population
Controlled studies						
103	II	Placebo Lisinopril	4 weeks	Valsartan 40 mg BID	24	HF patients, NYHA Class II - IV PCWP ≥ 15 mm Hg
				Valsartan 80 mg BID	24	
				Valsartan 160 mg BID	27	
				Placebo	26	
				Lisinopril 5 mg/10 mg OD	15	
104	II	Placebo	4 weeks	Valsartan 80 mg BID	28	HF patients, NYHA Class II - IV PCWP ≥ 15 mm Hg
				Valsartan 160 mg BID	27	
				Placebo	28	
106	III	Placebo	16 weeks	Valsartan 40 mg BID	185	HF patients, NYHA Class II - IV Ejection fraction < 40%
				Valsartan 80 mg BID	195	
				Valsartan 160 mg BID	198 ^{1,2}	
				Total valsartan	578 ²	
				Placebo	192	
107*	III	Placebo	Up to 185 weeks	Total valsartan (40/80/160 mg BID)	2511 ³	HF patients, NYHA Class II - IV Ejection fraction ≤ 40% LVIDD > 2.9 cm/m ²
				Placebo	2499 ⁴	
110*	III	Enalapril	12 weeks	Valsartan 80 mg OD force titrated to 160 mg OD	70	HF patients, NYHA Class II - III Ejection fraction ≤ 45%
				Enalapril 5 mg BID force titrated to 10 mg BID	71	
Total randomized to valsartan				3289		
Total randomized to enalapril				71		
Total randomized to lisinopril				15		
Total randomized to placebo				2745		

*Forced titration study

¹In Study 106, 198 patients randomized to the 160 mg BID group received 80 mg BID for one week, then were to be titrated to the higher dose.

²Includes 1 patient who was randomized to valsartan 160 mg BID group, but never received study medication.

³Includes 3 patients who were randomized to valsartan, but never received study medication.

⁴Includes 2 patients who were randomized to placebo, but never received study medication.

4.2. Population evaluated

4.2.1. Demographics

A summary of the demographic characteristics for the primary dataset is shown in Table 4-2. Although the number of patients in the active treatment groups is small relative to the numbers in the valsartan and placebo groups, the demographic variables are generally similar across treatment groups. Overall, slightly more than half of the patients in the valsartan and placebo groups were younger than 65 years of age, with a mean age of approximately 63 years. Approximately 90% of the valsartan and placebo patients were white, and approximately 80% were males.

Table 4-2. Summary of demographic characteristics (primary dataset)

	Valsartan (total daily dose)				Active control ² N = 86 n (%)	Placebo N = 2745 n (%)
	0 mg N = 473 n (%)	80 mg N = 2787 n (%)	160 mg N = 2844 n (%)	320 mg N = 2304 n (%)	All ¹ N = 3289 n (%)	
Age (mean years)	63.9	62.5	62.7	62.5	62.5	63.0
Age group						
< 65 years	234 (49.5)	1506 (54.0)	1523 (53.6)	1245 (54.0)	1773 (53.9)	1431 (52.1)
≥ 65 years	239 (50.5)	1281 (46.0)	1320 (46.4)	1059 (46.0)	1516 (46.1)	1314 (47.9)
≥ 75 years	79 (16.7)	366 (13.1)	386 (13.6)	294 (12.8)	451 (13.7)	416 (15.2)
Race						
White	416 (87.9)	2502 (89.8)	2522 (88.7)	2028 (88.0)	2918 (88.7)	2475 (90.2)
Black	38 (8.0)	204 (7.3)	234 (8.2)	199 (8.6)	271 (8.2)	190 (6.9)
Oriental/Other	19 (4.0)	81 (2.9)	87 (3.1)	77 (3.3)	100 (3.0)	80 (2.9)
Sex						
Male	366 (77.4)	2217 (79.5)	2269 (79.8)	1840 (79.9)	2639 (80.2)	2205 (80.3)
Female	107 (20.5)	570 (20.5)	574 (20.2)	464 (20.1)	650 (19.8)	540 (19.7)

The primary dataset consisted of Studies 103, 104, 106, 107 (first 4 months) and 110

¹Patients may be counted in more than one valsartan dose group, but only once in the "all" column. In Study 107, the valsartan treatment interruptions during the double-blind period were captured in the 0 mg group and were included in the "all" column.

²Combines lisinopril and enalapril treatment groups

Disease characteristics of the key safety population

A summary of baseline disease characteristics for the primary dataset is provided in Table 4-3. Baseline background cardiovascular therapy is summarized in Table 4-4. As expected, nearly all patients were in NYHA Class II or III at baseline, with approximately 61% in Class II. The majority of patients had coronary heart disease as their HF etiology. The vast majority of valsartan and placebo patients had taken ACE inhibitors, diuretics and digoxin as background treatment at or prior to randomization. No meaningful differences in disease characteristics were observed across treatment groups.

Table 4-3. Summary of baseline disease characteristics (primary dataset)

	Valsartan (total daily dose)					Active control ² N = 86 n (%)	Placebo N = 2743 n (%)
	0 mg N = 473 n (%)	80 mg N = 2787 n (%)	160 mg N = 2843 n (%)	320 mg N = 2304 n (%)	All ¹ N = 3289 n (%)		
Duration of HF (mean months)	52.0	50.5	50.4	50.5	50.5	52.0	51.2
LVEF ³ (mean %)	26.2	26.6	26.7	26.8	26.6	--	26.9
Weight (mean kg)	78.5	80.0	80.5	80.1	80.7	82.1	79.3
NYHA Classification							
I	1 (0.2)	2 (0.1)	4 (0.1)	3 (0.1)	4 (0.1)	0 (0)	5 (0.2)
II	252 (53.3)	1724 (61.9)	1761 (61.9)	1466 (63.6)	2006 (61.0)	56 (65.1)	1660 (60.5)
III	206 (43.6)	1015 (36.4)	1037 (36.5)	804 (34.9)	1221 (37.1)	27 (31.4)	1021 (37.2)
IV	14 (3.0)	46 (1.7)	41 (1.4)	31 (1.3)	58 (1.8)	3 (3.5)	59 (2.1)
HF Etiology ⁴	N = 473	N = 2763	N = 2819	N = 2277	N = 3214	N = 71	N = 2719
Coronary heart disease	292 (61.7)	1589 (57.5)	1620 (57.4)	1286 (56.5)	1842 (57.3)	39 (54.9)	1546 (56.9)
Idiopathic cardiomyopathy	133 (28.1)	861 (31.2)	866 (30.7)	708 (31.1)	985 (30.6)	26 (36.6)	825 (30.3)
Hypertension	18 (3.8)	171 (6.2)	187 (6.6)	167 (7.3)	212 (6.6)	1 (1.4)	210 (7.7)
Other	30 (6.3)	142 (5.1)	147 (5.2)	116 (5.1)	175 (5.4)	5 (7.0)	138 (5.1)

The primary dataset consisted of Studies 103, 104, 106, 107 (first 4 months) and 110

¹Patients may be counted in more than one valsartan dose group, but only once in the "all" column. In Study 107, the valsartan treatment interruptions during the double-blind period were captured in the 0 mg group and were included in the "all" column.

²Combines lisinopril and enalapril treatment groups.

³Not available for Studies 103, 104 and 110

⁴Does not include Study 103, which allowed multiple etiology selections

Table 4-4. Summary of baseline background cardiovascular therapy (primary dataset)

	Valsartan (total daily dose)				All ¹ N = 3289 n (%)	Active control ² N = 86 n (%)	Placebo N = 2743 n (%)
	0 mg N = 473 n (%)	80 mg N = 2787 n (%)	160 mg N = 2843 n (%)	320 mg N = 2304 n (%)			
Use of background treatment at or prior to randomization							
ACE inhibitors	433 (91.5)	2493 (89.5)	2524 (88.8)	2097 (91.0)	2887 (87.8)	2 (2.3)	2511 (91.5)
Diuretics	426 (90.1)	2385 (85.6)	2422 (85.2)	1957 (84.9)	2807 (85.3)	69 (80.2)	2326 (84.7)
Digoxin	349 (73.8)	1846 (66.2)	1887 (66.4)	1543 (67.0)	2195 (66.7)	38 (44.2)	1853 (67.5)
Nitrates (long and short-acting)	209 (44.2)	1046 (37.5)	1048 (36.9)	847 (36.8)	1174 (35.7)	25 (29.1)	1015 (37.0)
Beta blockers	151 (31.9)	975 (35.0)	959 (33.7)	760 (33.0)	1074 (32.7)	55 (64.0)	930 (33.9)
Amiodarone	62 (13.1)	341 (12.2)	360 (12.7)	294 (12.8)	401 (12.2)	5 (5.8)	359 (13.1)
Calcium channel blockers	59 (12.5)	305 (10.9)	313 (11.0)	259 (11.2)	347 (10.6)	1 (1.2)	337 (12.3)

The primary dataset consisted of Studies 103, 104, 106, 107 (first 4 months) and 110

¹Patients may be counted in more than one valsartan dose group, but only once in the "all" column. In Study 107, the valsartan treatment interruptions during the double-blind period were captured in the 0 mg group and were included in the "all" column.

²Combines lisinopril and enalapril treatment groups.

4.2.2. Extent of exposure

Table 4-5 presents the number of patients with minimum exposure in days by total daily dose for Study 107, which was the study that contributed the majority of the patients to the integrated safety analysis. This shows that the guidelines for long-term exposure were met; ie, the number of valsartan-treated patients exposed for at least 6 months, 12 months and 2 years were 2155, 1968 and 1061, respectively.

Table 4-5. Number of patients with minimum exposure (days) by total daily dose (Study 107)

No. of days	Valsartan (total daily dose)				All ¹	Placebo
	0 mg	80 mg	160 mg	320 mg		
≥ 1	1191	2508	2342	2118	2508	2497
≥ 30	540	461	525	1944	2409	2428
≥ 60	361	310	396	1900	2323	2371
≥ 90	228	276	344	1848	2268	2330
≥ 180	67	224	268	1693	2155	2235
≥ 360	9	162	199	1543	1968	2063
≥ 720	0	69	77	722	1061	1108

¹Patients may be counted in more than one valsartan dose group, but only once in the "all" column. Valsartan treatment interruptions during the double-blind period were captured in the 0 mg group and were excluded from the "all" column.

4.3. Adverse events

4.3.1. Most frequently affected body systems and most frequent adverse events

Table 4-6 lists those body systems for which greater than 10% of valsartan treated patients experienced an adverse event related to that body system as reported for the all-controlled short-term trials (primary dataset).

Table 4-6. No. of patients with adverse events in the most frequently affected body systems ($\geq 10\%$ in the valsartan group) whether or not study drug related, all-controlled short-term trials (primary dataset)

	Valsartan n (%)	Active Control ¹ n (%)	Placebo n (%)
Patients studied			
Total no. of patients (SAP)	3282 (100)	86 (100)	2740 (100)
Total no. of patients with AEs	2380 (72.5)	53 (61.6)	1876 (68.5)
Body system affected			
Nervous system disorders	895 (27.3)	9 (10.5)	526 (19.2)
Infections/Infestations	688 (21.0)	15 (17.4)	578 (21.1)
Gastrointestinal disorders	573 (17.5)	8 (9.3)	454 (16.6)
General disorders and administration site conditions	517 (15.8)	6 (7.0)	432 (15.8)
Cardiac disorders	477 (14.5)	6 (7.0)	452 (16.5)
Vascular disorders	401 (12.2)	2 (2.3)	190 (6.9)
Respiratory disorders	398 (12.1)	3 (3.5)	355 (13.0)
Musculoskeletal, connective tissue/ bone disorders	397 (12.1)	10 (11.6)	277 (10.1)
Metabolism/nutrition disorders	345 (10.5)	2 (2.3)	234 (8.5)

¹enalapril or lisinopril

Studies included: 103,104, 106, 110 and 107 up to and including visit 7

These rates were generally comparable to placebo with the exception of nervous system disorders and vascular disorders, where the incidence of occurrence was higher in the valsartan group compared with the placebo group.

Table 4-7 presents those body systems for which $\geq 20\%$ of valsartan-treated patients experienced an adverse event related to that body system for Study 107.

Table 4-7. No. of patients with adverse events in the most frequently affected body systems ($\geq 20\%$ in the valsartan group) whether or not study drug related, placebo-controlled long-term trial (dataset C)

	Valsartan n (%)	Placebo n (%)
Patients studied		
Total no. of patients (SAP)	2506 (100)	2494 (100)
Total no. of patients with AEs	2295 (91.6)	2235 (89.6)
Body system affected		
Infections/infestations	1100 (43.9)	1155 (46.3)
Nervous system disorders	1056 (42.1)	923 (37.0)
Cardiac disorders	969 (38.7)	1152 (46.2)
General disorders and administration site conditions	898 (35.8)	907 (36.4)
Gastrointestinal disorders	877 (35.0)	867 (34.8)
Respiratory disorders	685 (27.3)	776 (31.1)
Vascular disorders	677 (27.0)	516 (20.7)
Musculoskeletal, connective tissue/ bone disorders	672 (26.8)	646 (25.9)
Metabolism/nutrition disorders	668 (26.7)	583 (23.4)

Studies included: 107

As for the primary dataset, the incidence of nervous system and vascular system adverse events was slightly increased in the valsartan group. Conversely, the placebo group had a slightly higher incidence of cardiac disorders.

There were no clinically relevant differences in adverse event rates by body system between valsartan and placebo.

The following discussion is focussed on patients reporting at least one adverse event during treatment, whether or not study drug related. The patients included in these studies, in addition to taking valsartan, have been optimally treated with other heart failure medications including ACE inhibitors, beta-blockers, diuretics, digoxin and other medications which act on the RAS (ie spironolactone). In light of this combined therapy, it is not unexpected that these patients experience effects that are directly related to inhibiting the RAS, such as signs and symptoms of hypotension (dizziness, syncope, orthostatic changes) and effects on the renal system (increased BUN, potassium and creatinine). In general, these effects are not exclusive to valsartan, but may be expected with multiple drug therapies used to treat heart failure.

Table 4-8 shows the incidence of the 20 most frequently reported adverse events in $\geq 2\%$ of patients in the valsartan group for the primary dataset. Table 4-9 shows the most frequently reported adverse events in $\geq 5\%$ of patients in the valsartan group for Study 107. Adverse events are listed by order of frequency in the valsartan group.

Table 4-8. No. of patients with most frequent adverse events ($\geq 2\%$ in the valsartan group) whether or not study drug related, all-controlled short-term trials (primary dataset)

	Valsartan n (%)	Active Control n (%)	Placebo n (%)
Patients studied			
Total no. of patients (SAP)	3282(100)	86 (100)	2740 (100)
Total no. of patients with an AE	2380 (72.5)*	53 (61.6)	1876 (68.5)
Adverse Events			
Dizziness (exc vertigo)	568 (17.3)*	7 (8.1)	255 (9.3)
Hypotension NOS	218 (6.6)*	0 (0.0)	65 (2.4)
Chest pain NEC	168 (5.1)	1 (1.2)	153 (5.6)
Cough	157 (4.8)	2 (2.3)	135 (4.9)
Diarrhea NOS	148 (4.5)	2 (2.3)	100 (3.6)
Nasopharyngitis	146 (4.4)	6 (7.0)	107 (3.9)
Upper respiratory tract infection NOS	144 (4.4)	2 (2.3)	116 (4.2)
Nausea	137 (4.2)	1 (1.2)	106 (3.9)
Headache NOS	132 (4.0)	1 (1.2)	116 (4.2)
Arthralgia	90 (2.7)	1 (1.2)	58 (2.1)
Fatigue	89 (2.7)*	2 (2.3)	52 (1.9)
Back pain	86 (2.6)	4 (4.7)	51 (1.9)
Congestive cardiac failure aggravated	83 (2.5)	0 (0.0)	90 (3.3)
Dizziness postural	81 (2.5)*	0 (0.0)	32 (1.2)
Influenza	80 (2.4)	0 (0.0)	62 (2.3)
Pain in limb	80 (2.4)	1 (1.2)	64 (2.3)
Hyperkalemia	79 (2.4)*	0 (0.0)	29 (1.1)
Angina pectoris	76 (2.3)	1 (1.2)	58 (2.1)
Insomnia NEC	70 (2.1)	0 (0.0)	57 (2.1)
Postural hypotension	68 (2.1)*	0 (0.0)	20 (0.7)

Studies included: 103,104, 106, 110 and 107 up to and including visit 7

* statistically significant ($p < 0.05$), valsartan compared with placebo

Table 4-9. No. of patients with most frequent adverse events ($\geq 5\%$ in the valsartan group) whether or not study drug related, placebo-controlled long-term trial (Study 107)

	Valsartan n (%)	Placebo n (%)
Patients studied		
Total no. of patients (SAP)	2506 (100)	2494 (100)
Total no. of patients with an AE	2295 (91.6)*	2235 (89.6)
Adverse Events		
Dizziness (exc vertigo)	627 (25.0)*	451 (18.1)
Hypotension NOS	347 (13.8)*	201 (8.1)
Chest pain NEC	337 (13.4)	352 (14.1)
Congestive cardiac failure aggravated	276 (11.0)	387 (15.5)*
Cough	257 (10.3)	267 (10.7)
Nasopharyngitis	250 (10.0)	229 (9.2)
Upper respiratory tract infection NOS	244 (9.7)	260 (10.4)
Diarrhea NOS	238 (9.5)*	193 (7.7)
Nausea	218 (8.7)	236 (9.5)
Bronchitis NOS	196 (7.8)	210 (8.4)
Arthralgia	195 (7.8)	172 (6.9)
Influenza	184 (7.3)	173 (6.9)
Headache NOS	171 (6.8)	182 (7.3)
Angina pectoris	164 (6.5)	165 (6.6)
Hyperkalemia	163 (6.5)*	81 (3.2)
Pain in limb	154 (6.1)	146 (5.9)
Back pain	145 (5.8)	122 (4.9)
Renal impairment NOS	135 (5.4)*	76 (3.0)
Sudden death unexplained	135 (5.4)	153 (6.1)
Atrial fibrillation	132 (5.3)	196 (7.9)*
Insomnia NEC	128 (5.1)	157 (6.3)
Gout	125 (5.0)	113 (4.5)
Ventricular tachycardia	125 (5.0)	119 (4.8)

* Statistically significant ($p < 0.05$), valsartan compared with placebo

Adverse events by severity

Adverse experiences were summarized by severity in order to assess the potential of the study drugs to cause severe adverse effects. The relative severities of the five most frequently reported adverse events in the valsartan group, whether or not study drug related, are displayed for the primary dataset in Table 4-10. Since the active control group contributed too few patients to provide a meaningful comparison, those data are not presented.

Table 4-10. Incidence of the five most frequently reported adverse experiences (in the valsartan group), whether or not study drug related by severity for the primary dataset

	Valsartan n (%)	Placebo n (%)
Total patients (SAP)	3282 (100)	2740 (100)
Total no. of patients with AEs	2380 (72.5)	1876 (68.5)
Total no. of patients with severe AEs	535 (16.3)	422 (15.4)
Dizziness (exc vertigo)		
Mild	324 (9.9)	156 (5.7)
Moderate	209 (6.4)	82 (3.0)
Severe	35 (1.1)	17 (0.6)
Hypotension NOS		
Mild	79 (2.4)	22 (0.8)
Moderate	101 (3.1)	24 (0.9)
Severe	38 (1.2)	19 (0.7)
Chest pain NEC		
Mild	73 (2.2)	74 (2.7)
Moderate	74 (2.3)	60 (2.2)
Severe	21 (0.6)	19 (0.7)
Cough		
Mild	107 (3.3)	80 (2.9)
Moderate	45 (1.4)	51 (1.9)
Severe	5 (0.2)	4 (0.1)
Diarrhea NOS		
Mild	83 (2.5)	48 (1.8)
Moderate	58 (1.8)	42 (1.5)
Severe	7 (0.2)	10 (0.4)

Studies included: 103,104, 106, 110 and 107 up to and including visit 7

Adverse events suspected to be study drug related

Adverse events were classified as suspected study drug related based on the investigators' opinion. Any adverse event considered possibly, probably, or highly probably related to study drug by the investigator is classified as "suspected study drug related". Generally, less than half of the overall adverse events were considered study drug related by the investigators. As previously noted, the general heart failure population in these studies have been optimally treated with other heart failure medications including ACE inhibitors, beta-blockers, diuretics, digoxin and other medications which act on the RAS (ie spironolactone). With this combination of therapy it is not unexpected that these patients will experience effects that are directly related to inhibiting the RAS, such as signs and symptoms of hypotension (dizziness, syncope, orthostatic changes) and effects on the renal system (increased BUN, potassium and creatinine).

Table 4-11 displays the most frequent adverse events in the primary dataset that were considered to be study drug related by the investigator in $\geq 1\%$ of valsartan treated patients.

Table 4-11. No. of patients with most frequent adverse events ($\geq 1\%$ in the valsartan group), suspected study drug related by investigator for all- controlled short-term trials (primary dataset)

	Valsartan n (%)	Active Control n (%)	Placebo n (%)
Patients Studied			
Total no. of patients (SAP)	3282 (100)	86 (100)	2740 (100)
Total no. of patients with an AE	1063 (32.4)*	18 (20.9)	549 (20.0)
Adverse Events			
Dizziness (exc vertigo)	430 (13.1)*	4 (4.7)	159 (5.8)
Hypotension NOS	180 (5.5)*	0 (0.0)	48 (1.8)
Dizziness postural	72 (2.2)*	0 (0.0)	26 (0.9)
Postural hypotension	61 (1.9)*	0 (0.0)	13 (0.5)
Fatigue	54 (1.6)	1 (1.2)	29 (1.1)
Diarrhea NOS	51 (1.6)*	1 (1.2)	21 (0.8)
Headache NOS	50 (1.5)	1 (1.2)	37 (1.4)
Nausea	50 (1.5)	1 (1.2)	29 (1.1)
Renal impairment NOS	49 (1.5)*	1 (1.2)	10 (0.4)
Hyperkalemia	42 (1.3)*	0 (0.0)	14 (0.5)
Vertigo NEC	38 (1.2)*	2 (2.3)	13 (0.5)
Cough	35 (1.1)	1 (1.2)	29 (1.1)
Syncope	34 (1.0)*	0 (0.0)	14 (0.5)

Studies included: 103,104, 106, 110 and 107 up to and including visit 7

*Statistically significant ($p < 0.05$), valsartan compared with placebo

Table 4-12 displays the most frequent adverse events considered to be study drug related by the investigator in $\geq 1\%$ of valsartan treated patients in the long-term placebo-controlled Study 107.

Table 4-12. No. of patients with most frequent adverse events (≥1% in the valsartan group), suspected study drug related by investigator for placebo-controlled long-term trial (dataset C)

	Valsartan n (%)	Placebo n (%)
Patients Studied		
Total no. of patients (SAP)	2506 (100)	2494 (100)
Total no. of patients with an AE	1152 (46.0)*	807 (32.4)
Adverse Events		
Dizziness (exc vertigo)	442 (17.6)*	226 (9.1)
Hypotension NOS	242 (9.7)*	109 (4.4)
Renal impairment NOS	98 (3.9)*	40 (1.6)
Hyperkalemia	90 (3.6)*	26 (1.0)
Dizziness postural	71 (2.8)*	36 (1.4)
Postural hypotension	71 (2.8)*	27 (1.1)
Fatigue	51 (2.0)	36 (1.4)
Diarrhea NOS	49 (2.0)*	25 (1.0)
Nausea	47 (1.9)	39 (1.6)
Syncope	47 (1.9)	33 (1.3)
Headache NOS	46 (1.8)	40 (1.6)
Blood creatinine increase	44 (1.8)*	16 (0.6)
Vertigo NEC	43 (1.7)*	16 (0.6)
Cough	41 (1.6)	41 (1.6)
Weakness	25 (1.0)	22 (0.9)
Vision blurred	25 (1.0)*	6 (0.2)

Studies included: 107

* Statistically significant ($p < 0.05$), valsartan compared with placebo

Dose-related adverse events

Since the majority of patients were in forced titration trials and the duration of therapy was different for each dose level, it was difficult to interpret dose response in any integrated dataset. In Study 106, however, possible dose-related effects were observed in the analysis of adverse events for the incidence of hyperkalemia. Table 4-13. displays the most frequently reported adverse events occurring outside the exercise tolerance test (ETT) for study 106.

Table 4-13. Number (%) of patients with non-ETT AEs overall ($\geq 3\%$ for any group), whether or not study drug related, for study 106

	Valsartan n (%)				Placebo n (%)
	80 mg	160 mg	320 mg	all	all
Patients studied					
Total no. of patients (SAP)	185	194	197	576	192
Total no. of patients with a non-ETT AEs	134 (72.4)	147 (75.8)	153 (77.7)	434 (75.3)	149 (77.6)
Adverse events					
Dizziness (exc vertigo)	38 (20.5)	31 (16.0)	27 (13.7)	96 (16.7)	22 (11.5)
Chest pain NEC	13 (7.0)	15 (7.7)	17 (8.6)	45 (7.8)	15 (7.8)
Hypotension NOS	14 (7.6)	12 (6.2)	8 (4.1)	34 (5.9)	2 (1.0)
Upper respiratory tract infection NOS	9 (4.9)	10 (5.2)	11 (5.6)	30 (5.2)	15 (7.8)
Diarrhea NOS	9 (4.9)	8 (4.1)	12 (6.1)	29 (5.0)	10 (5.2)
Nasopharyngitis	6 (3.2)	12 (6.2)	10 (5.1)	28 (4.9)	10 (5.2)
Cough	8 (4.3)	13 (6.7)	7 (3.6)	28 (4.9)	13 (6.8)
Nausea	13 (7.0)	9 (4.6)	5 (2.5)	27 (4.7)	9 (4.7)
Back pain	10 (5.4)	9 (4.6)	7 (3.6)	26 (4.5)	8 (4.2)
Headache NOS	13 (7.0)	7 (3.6)	6 (3.0)	26 (4.5)	9 (4.7)
Insomnia NEC	6 (3.2)	10 (5.2)	8 (4.1)	24 (4.2)	7 (3.6)
Fatigue	5 (2.7)	5 (2.6)	13 (6.6)	23 (4.0)	3 (1.6)
Pain in limb	8 (4.3)	11 (5.7)	4 (2.0)	23 (4.0)	5 (2.6)
Arthralgia	5 (2.7)	9 (4.6)	7 (3.6)	21 (3.6)	6 (3.1)
Muscle cramps	4 (2.2)	8 (4.1)	6 (3.0)	18 (3.1)	3 (1.6)
Influenza	3 (1.6)	7 (3.6)	6 (3.0)	16 (2.8)	7 (3.6)
Cardiac failure congestive	4 (2.2)	8 (4.1)	4 (2.0)	16 (2.8)	7 (3.6)
Syncope	5 (2.7)	7 (3.6)	3 (1.5)	15 (2.6)	3 (1.6)
Dizziness postural	2 (1.1)	4 (2.1)	8 (4.1)	14 (2.4)	3 (1.6)
Hyperkalemia	2 (1.1)	5 (2.6)	7 (3.6)	14 (2.4)	2 (1.0)
Sinusitis NOS	2 (1.1)	7 (3.6)	5 (2.5)	14 (2.4)	3 (1.6)
Palpitations	3 (1.6)	4 (2.1)	6 (3.0)	13 (2.3)	7 (3.6)
Weakness	2 (1.1)	6 (3.1)	5 (2.5)	13 (2.3)	6 (3.1)
Bronchitis NOS	1 (0.5)	3 (1.5)	6 (3.0)	10 (1.7)	6 (3.1)

Studies included: 106

Source: Clinical study report Post-text tables 10.1-1a and 10.1-1b

Most patients experienced at least one non-ETT adverse event (ie, those that did not occur during exercise tolerance testing), and the percentages of all adverse events were similar across treatment groups. Dizziness (exc vertigo) was the most frequently reported adverse event in all the treatment groups. Slightly higher rates of dizziness, hyperkalemia and hypotension NOS were reported in the valsartan groups compared to the placebo group. Although low in incidence, there is a suggestion of a dose relationship for hyperkalemia. The incidence rates of this event were 1.1%, 2.6% and 3.6% for valsartan 40 mg BID, valsartan 80 mg BID and valsartan 160 mg BID, respectively, versus 1.0% for placebo. Also, patients in the valsartan 160 mg bid group had slightly higher rates of fatigue than all other treatment groups.

4.3.2. Deaths and other serious or clinically significant adverse events

Deaths

A total of 19 deaths occurred during the double-blind controlled short-term trials, as shown in Table 4-14. The small number of deaths prevents meaningful comparison regarding individual causes of death. The most frequently reported cause of death in all treatment groups was unexplained sudden death (valsartan 0.3%; active control 2.3%; placebo 0.8%). Otherwise, most of the deaths were of cardiac causes. None of the deaths that occurred in valsartan-treated patients were suspected to be related to study drug (as described in the individual clinical study reports). Four of the deaths that occurred in enalapril-treated patients in Study 110 were suspected to be related to study drug.

Table 4-14. Deaths by principal cause assessed by investigator (double-blind controlled short-term trials 103, 104, 106 and 110)

	Valsartan n (%)	Active control ¹ n (%)	Placebo n (%)
Total number of randomized patients	778 (100)	86 (100)	246 (100)
Number of patients who died	10 (1.3)	5 (5.8)	4 (1.6)
Cardiac failure congestive	4 (0.5)	0 (0)	0 (0)
Sudden death unexplained	2 (0.3)	2 (2.3)	2 (0.8)
Cardiac arrest	2 (0.3)	0 (0)	0 (0)
Cerebrovascular accident NOS	1 (0.1)	0 (0)	0 (0)
Intestinal infarction	1 (0.1)	0 (0)	0 (0)
Cardiac failure NOS	0 (0)	1 (1.2)	0 (0)
Myocardial infarction	0 (0)	1 (1.2)	1 (0.4)
Pneumonia NOS	0 (0)	1 (1.2)	0 (0)
Ventricular fibrillation	0 (0)	0 (0)	1 (0.4)

¹Enalapril or lisinopril

In Study 106, 8 patients (2 placebo-treated and 6 valsartan-treated) died either after being discontinued, or within 30 days after completing the study. None were suspected to be related to study medication and all except one (lung cancer) were cardiovascular related.

The number and percentage of deaths in Study 107 are shown in Table 4-15. The overall incidence rates (valsartan 20.1%; placebo 20.0%) and individual causes of death were similar for both treatment groups. These were predominantly cardiovascular related, and not unexpected in this patient population. The most common cause of death in both groups was sudden death - unexpected, instantaneous or during sleep (valsartan 7.7%; placebo 7.1%).

Table 4-15. Number of deaths by principal cause assessed by investigator (Study 107)

Principal cause of death	Valsartan n (%)	Placebo n (%)
Total number of randomized patients	2511 (100)	2499 (100)
Total deaths	505 (20.1)	499 (20.0)
Sudden death - unexpected, instantaneous or during sleep (observed or presumed)	194 (7.7)	177 (7.1)
Pump failure, progressive CHF even if terminal event was arrhythmia or vascular event	143 (5.7)	130 (5.2)
Other non-cardiovascular event	43 (1.7)	34 (1.4)
Sudden death - premonitory worsening, CHF	22 (0.9)	34 (1.4)
Non-cardiovascular event - cancer	20 (0.8)	24 (1.0)
Unknown	15 (0.6)	22 (0.9)
Other vascular event	15 (0.6)	24 (1.0)
Acute myocardial infarction - documented	14 (0.6)	11 (0.4)
Vascular event - stroke	13 (0.5)	6 (0.2)
Acute myocardial infarction - presumed	12 (0.5)	18 (0.7)
Sudden death - premonitory worsening, arrhythmia	6 (0.2)	13 (0.5)
Sudden death - premonitory worsening, ischemia	6 (0.2)	3 (0.1)
Vascular event - cardiac procedure	2 (0.1)	3 (0.1)

Serious adverse events

The overall incidence rates of SAEs, as well as the most frequently occurring ($\geq 1\%$) individual SAEs in the primary dataset are shown in Table 4-16. No clinically relevant differences were observed between treatment groups for the overall or individual SAE rates. The most frequently reported SAE was congestive cardiac failure aggravated (valsartan 2.0%; placebo 2.9%). None of the events shown in Table 4-16 were unexpected in the study population.

Table 4-16. Number (%) of patients with SAEs ($\geq 1\%$ for any group) (primary dataset)

	Valsartan N = 3282 n (%)	Active control¹ N = 86 n (%)	Placebo N = 2740 n (%)
All SAEs	548 (16.7)	11 (12.8)	490 (17.9)
Congestive cardiac failure aggravated	66 (2.0)	0	79 (2.9)
Chest pain NEC	31 (0.9)	1 (1.2)	36 (1.3)
Hypotension NOS	32 (1.0)	0	15 (0.5)
Myocardial infarction	25 (0.8)	2 (2.3)	15 (0.5)
Ventricular tachycardia	26 (0.8)	0	20 (0.7)
Cardiac arrest	22 (0.7)	0	18 (0.7)
Sudden death unexplained	24 (0.7)	2 (2.3)	30 (1.1)
Pneumonia NOS	21 (0.6)	1 (1.2)	24 (0.9)
Atrial fibrillation	21 (0.6)	0	24 (0.9)
Renal impairment NOS	11 (0.3)	1 (1.2)	1 (0.0)
Ventricular fibrillation	8 (0.2)	1 (1.2)	10 (0.4)
Urinary tract infection NOS	2 (0.1)	1 (1.2)	5 (0.2)
Hypersensitivity NOS	0	1 (1.2)	0
Viral infection NOS	0	1 (1.2)	0

The primary dataset consisted of Studies 103, 104, 106, 107 (first 4 months) and 110

¹Combines lisinopril and enalapril treatment groups

In addition to the events included in Table 4-16, other SAEs that are of concern in this patient population and with angiotensin receptor blockers taken in combination with standard HF therapy include hyperkalemia, renal failure, postural hypotension and dizziness. The following SAEs all occurred at very low frequencies in the primary dataset, but generally at slightly higher rates in the valsartan group (all doses combined) versus placebo [n (%)]:

postural hypotension: valsartan 8 (0.2); placebo 2 (0.1)

dizziness excluding vertigo: valsartan 18 (0.5); placebo 6 (0.2)

hyperkalemia: valsartan 16 (0.5); placebo 4 (0.1)

renal failure acute: valsartan 15 (0.5); placebo 4 (0.1)

increased creatinine: valsartan 9 (0.3); placebo 0

renal failure NOS: valsartan 7 (0.2); placebo 3 (0.1)

renal failure aggravated: valsartan 0; placebo 1 (0.0)

The overall incidence rates of SAEs, as well as the most frequently occurring ($\geq 2\%$) individual SAEs in Study 107 are shown in Table 4-17. Across treatment groups, the overall SAE rates were higher for Study 107 (valsartan 51.2%; placebo 53.8%) than for the primary dataset, but no clinically relevant differences were observed between treatment groups for the overall or individual SAE rates. The most frequently reported individual SAE in Study 107 was congestive cardiac failure aggravated (valsartan 9.2%; placebo 13.3%) followed by sudden death unexplained (valsartan 5.4%; placebo 6.1%) and chest pain (4.8% for both groups).

Some SAEs occurred at slightly higher frequencies with placebo than with valsartan (all doses): congestive cardiac failure aggravated, pneumonia, atrial fibrillation, cardiac failure aggravated, angina unstable, cardiac failure NOS, and dyspnea NOS. These events were not unexpected in the study population.

Table 4-17. Number (%) of patients with SAEs ($\geq 2\%$ for any group) (Study 107)

	Valsartan N = 2506 n (%)	Placebo N = 2494 n (%)
All SAEs	1282 (51.2)	1342 (53.8)
Congestive cardiac failure aggravated	231 (9.2)	331 (13.3)
Sudden death unexplained	135 (5.4)	152 (6.1)
Chest pain NEC	120 (4.8)	120 (4.8)
Ventricular tachycardia	84 (3.4)	77 (3.1)
Myocardial infarction	83 (3.3)	72 (2.9)
Pneumonia NOS	63 (2.5)	79 (3.2)
Syncope	62 (2.5)	60 (2.4)
Angina pectoris	63 (2.5)	49 (2.0)
Atrial fibrillation	59 (2.4)	98 (3.9)
Cardiac arrest	58 (2.3)	63 (2.5)
Hypotension NOS	55 (2.2)	48 (1.9)
Cardiac failure aggravated	52 (2.1)	91 (3.6)
Pulmonary edema NOS	53 (2.1)	58 (2.3)
Dehydration	49 (2.0)	33 (1.3)
Angina unstable	48 (1.9)	67 (2.7)
Cardiac failure NOS	42 (1.7)	65 (2.6)
Dyspnea NOS	40 (1.6)	58 (2.3)

Across datasets, very few SAEs were suspected to be study drug related, but the overall rates occurred at slightly higher frequencies with valsartan than with placebo, as shown in Table 4-18.

Table 4-18. Number (%) of patients with SAEs suspected to be related to study drug, by dataset and treatment group

All "suspected" SAEs	Valsartan n (%)	Active control ¹ n (%)	Placebo n (%)
Primary dataset	N = 3282 103 (3.1)	N = 86 5 (5.8)	N = 2740 53 (1.9)
Dataset B	N = 3212 103 (3.2)	N = 15 0 (0)	N = 2740 53 (1.9)
Study 107	N = 2506 192 (7.7)	--	N = 2494 135 (5.4)

The primary dataset consisted of Studies 103, 104, 106, 107 (first 4 months) and 110. Dataset B consisted of Studies 103, 104, 106, and 107 (first 4 months).

¹Combines lisinopril and enalapril treatment groups

In the primary dataset, and in dataset B, the most frequently reported SAEs suspected to be related to study drug were hypotension NOS, renal impairment NOS, syncope and dizziness (excluding vertigo), but none of these occurred at a frequency > 0.5% in any treatment group. In Study 107, the most frequently reported SAEs suspected to be related to study drug were renal impairment NOS (1.4% for valsartan; 0.3% for placebo), hypotension NOS (1.1% for valsartan; 0.7% for placebo) and hyperkalemia (0.9% for valsartan; 0.1% for placebo). These events are known to be associated with drugs that inhibit the renin angiotensin system.

One patient in Study 102 experienced a serious adverse experience during the trial. This patient (valsartan 160 mg treatment group) experienced a deterioration in his underlying congestive heart failure that was not related to trial medication.

There were no SAEs in Study 105.

Discontinuations due to adverse events

Discontinuations due to adverse events in >0.3% in the valsartan treated patients, whether or not study drug related, for the most frequent adverse events as reported for the all controlled short-term trials are displayed in Table 4-19.

Table 4-19. Incidence of discontinuations by adverse event (>0.3% in the valsartan group) for all-controlled short-term trials 103, 104, 106 and 110

	Valsartan n (%)	Active Control n (%)	Placebo n (%)
Patients studied			
Total no. of patients (SAP)	776 (100)	86 (100)	246 (100)
Total no. of patients discontinuing because of an AE	67 (8.6)	4 (4.7)	9 (3.7)
Adverse Events			
Hypotension NOS	19 (2.4)	0	0
Dizziness (exc vertigo)	17 (2.2)	0	0
Fatigue	6 (0.8)	0	0
Nausea	5 (0.6)	1 (1.2)	0
Pneumonia NOS	4 (0.5)	1 (1.2)	0
Diarrhea NOS	4 (0.5)	0	1 (0.4)
Vomiting NOS	4 (0.5)	1 (1.2)	0
Dyspnea NOS	4 (0.5)	0	0
Weakness	3 (0.4)	0	1 (0.4)
Renal failure acute	3 (0.4)	0	0

The incidence of discontinuation because of an adverse event was greater in the valsartan group compared to placebo. The most common adverse events leading to discontinuation from trial were dizziness (exc vertigo) and hypotension NOS. Overall, there were very few adverse events leading to discontinuation from trial.

In Study 107, patients were allowed discontinuation from trial treatment without discontinuation from trial. Table 4-19 displays the number of patients discontinuing from trial treatment due to an adverse event and the corresponding adverse event rate, whether or not study drug related, as presented in Table 4-10. The denominator for both number of patients who reported an adverse event and the number of patients discontinuing for an adverse event is the total number of patients studied (SAP).

As shown in Table 4-20, very few patients in either treatment group were discontinued due to an adverse event. Patients treated with valsartan had a slightly higher incidence of discontinuation due to an adverse event compared with the placebo group, (9.9% and 7.3% respectively).

Table 4-20. Adverse events ($\geq 5\%$ in the valsartan group) whether or not study drug related with corresponding incidence of discontinuations, by treatment and frequency for the placebo- controlled long-term trial (Study 107)

	Valsartan n (%)	Placebo n (%)		
Patients studied				
Total no. of patients (SAP)	2506 (100)	2494 (100)		
Total no. of patients with AEs	2295 (91.6)	2235 (89.6)		
Total no. of patients discontinuing because of an AE	249 (9.9)	181 (7.3)		
Adverse event	Adverse Event	Discontinued	Adverse Event	Discontinued
Dizziness (exc vertigo)	627 (25.0)	41 (1.6)	451 (18.1)	11 (0.4)
Hypotension NOS	347 (13.8)	32 (1.3)	201 (8.1)	20 (0.8)
Chest pain NEC	337 (13.4)	3 (0.1)	352 (14.1)	0
Congestive cardiac failure aggravated	276 (11.0)	9 (0.4)	387 (15.5)	18 (0.7)
Cough	257 (10.3)	7 (0.3)	267 (10.7)	4 (0.2)
Nasopharyngitis	250 (10.0)	0	229 (9.2)	0
Upper respiratory tract infection NOS	244 (9.7)	0	260 (10.4)	0
Diarrhea NOS	238 (9.5)	13 (0.5)	193 (7.7)	3 (0.1)
Nausea	218 (8.7)	10 (0.4)	236 (9.5)	7 (0.3)
Bronchitis NOS	196 (7.8)	0	210 (8.4)	0
Arthralgia	195 (7.8)	3 (0.1)	172 (6.9)	0
Influenza	184 (7.3)	0	173 (6.9)	0
Headache NOS	171 (6.8)	3 (0.1)	182 (7.3)	2 (0.1)
Angina pectoris	164 (6.5)	4 (0.2)	165 (6.6)	1 (0.0)
Hyperkalemia	163 (6.5)	13 (0.5)	81 (3.2)	2 (0.1)
Pain in limb	154 (6.1)	4 (0.2)	146 (5.9)	0
Back pain	145 (5.8)	0	122 (4.9)	1 (0.0)
Renal impairment NOS	135 (5.4)	27 (1.1)	76 (3.0)	6 (0.2)
Sudden death unexplained	135 (5.4)	0	153 (6.1)	0
Atrial fibrillation	132 (5.3)	1 (0.0)	196 (7.9)	2 (0.1)
Insomnia NEC	128 (5.1)	0	157 (6.3)	1 (0.0)
Gout	125 (5.0)	2 (0.1)	113 (4.5)	0
Ventricular tachycardia	125 (5.0)	2 (0.1)	119 (4.8)	4 (0.2)

The leading causes of discontinuation from trial treatment in Study 107 were dizziness (exc vertigo), hypotension NOS and renal impairment NOS. The difference in incidences between placebo and valsartan for the adverse events leading to discontinuations were very small. Overall the patients in the valsartan group reported a slightly higher incidence of adverse events; however, very few patients discontinued from trial treatment due to these adverse events. The discontinuations due to these causes were not unexpected as a consequence of inhibiting the renin-angiotensin-aldosterone system. Treatment with ACE inhibitors and angiotensin receptor blockers has been associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death in patients whose renal function may depend on the renin-angiotensin-aldosterone system (eg patients with severe heart failure).

Other clinically significant adverse events

Angioedema

The incidence rate of angioedema occurred at very low rates (0.1%) in all 3 datasets. It was reported for a total of 6 patients (one placebo and 5 valsartan-treated). Two cases occurred in Study 106 and 4 cases occurred in Study 107. None of these cases were considered serious adverse events. One case was suspected to be related to study medication and led to permanent discontinuation of study medication. All 6 patients were taking concomitant ACE inhibitors.

4.3.3. Adverse events in different population sub-groups

In the primary dataset and the long-term dataset (Study 107), the overall incidence of adverse events was generally unrelated to the race, gender, or age of the patients. In the long-term dataset (Study 107), the overall incidence of adverse events was generally unrelated to background use of ACE inhibitors or beta blockers at baseline.

4.4. Clinical laboratory data

Patients who participated in the clinical trials with valsartan had laboratory safety tests performed before the first dose of trial medication (baseline) and at periodic intervals during treatment. Laboratory tests were also performed at screening in the majority of the clinical trials.

The biochemistry parameters were SGPT (ALT), SGOT (AST), creatinine, alkaline phosphatase, total bilirubin, total protein, albumin, uric acid, glucose, sodium, potassium, chloride, phosphate, calcium, bicarbonate, BUN, total cholesterol, creatine kinase (CK, CPK), and LDH. The hematology parameters were hemoglobin, hematocrit, RBC, WBC, differential and platelet count. With the exception of Study 110, which had a limited laboratory profile, the majority of these laboratory parameters were evaluated in all of the controlled trials.

Biochemistry and hematology laboratory test results are presented as follows:

Summaries of changes from baseline to final laboratory test result (all parameters noted above except CK and LDH);

The number and percentage of patients exceeding a specified percent change from baseline to final laboratory test result [hemoglobin, hematocrit, WBC and absolute neutrophils; SGPT (ALT), SGOT (AST), creatinine, alkaline phosphatase, total bilirubin, uric acid, glucose, sodium, potassium, calcium and BUN].

All laboratory values from specimens obtained more than 24 hours after the last dose of trial medication were not included in any summary analyses, but are included in the individual patient data listings. Laboratory specimens that were hemolyzed, improperly centrifuged, or disrupted by improper handling were flagged in the database. Laboratory test values (eg potassium, SGOT, and SGPT) affected by one or more of these conditions were not included in any summary analyses, but were included in the individual patient data listing. In addition, potassium values ≥ 7 mEq/L were excluded from the primary summary analyses, as these

values were presumed implausible by the Novartis monitor, but were included in supplementary summaries for potassium.

Lastly, in Study 107, there were fewer than 100 individual laboratory test values (mostly serum phosphate) considered to be implausible by the Novartis monitor after consultation with the laboratory and most likely due to poor centrifugation. These values were also not included in any summary analyses but were included in the individual patient data listings.

The laboratory safety tests were evaluated at several different laboratories but the normal ranges were converted to U.S. reference units. Normal ranges used for these evaluations were those set by each of the central laboratories that contributed data. In general, these ranges were comparable when converted to U.S. reference units. Any differences in laboratory ranges apply across all treatment groups at a given laboratory. In addition, the different laboratories involved in the valsartan program may have used different methodologies to evaluate laboratory specimens. These possible differences must be taken into account when evaluating the data.

As normal ranges for a given laboratory test differ between laboratories and investigators differ on the magnitude of changes that are clinically meaningful, Ciba/Novartis set standards for percent changes from baseline to post-baseline values that were to be considered clinically meaningful for 15 laboratory tests; these are discussed below.

The results of the tests performed in the double-blind controlled short-term trials and long-term Study 107 are the primary focus of this section.

Biochemistry

The mean changes from baseline to final biochemistry parameter results are shown in Tables 4-21 (primary dataset, all parameters) and 4-22 (Study 107, selected parameters). The valsartan group had slightly higher mean increases in BUN than the active control group and/or the placebo group in all 3 datasets. Otherwise, mean and median values for all biochemistry variables and changes from baseline were clinically unremarkable and no clinically relevant differences between treatment groups were observed.

Table 4-21. Mean changes from baseline to final biochemistry parameter results (primary dataset)

Parameter	Valsartan	Active control ¹	Placebo
Creatinine (mg/dL)	0.1	0.0	0.0
Uric acid (mg/dL)	0.3	0.0	0.0
Potassium* (mEq/L)	0.1	0.1	0.0
BUN (mg/dL)	3.9	1.1	0.5
SGPT (ALT) (U/L)	-0.1	1.1	0.6
SGOT (AST) (U/L)	-0.4	-1.7	0.7
Alkaline phosphatase (U/L)	-3.1	17.8	2.5
Total bilirubin (mg/dL)	-0.1	0.0	0.0
Total protein (g/dL)	0.0	-0.3	0.0
Albumin (g/dL)	0.0	0.0	0.0
Glucose (mg/dL)	-0.4	1.3	-0.2
Sodium (mEq/L)	-0.2	-0.1	-0.2
Chloride (mEq/L)	0.6	-0.2	0.0
Phosphate (mg/dL)	0.0	0.2	0.0
Calcium (mg/dL)	0.0	0.3	0.0
Bicarbonate (mEq/L)	-0.6	-0.3	-0.1
Cholesterol (mg/dL)	0.2	0.2	-4.3

The primary dataset consisted of Studies 103, 104, 106, 107 (first 4 months) and 110

¹Combines lisinopril and enalapril treatment groups

*excluding values ≥ 7 mEq/L

Table 4-22. Mean changes from baseline to final selected biochemistry parameter results (Study 107)

Parameter	Valsartan	Placebo
Creatinine (mg/dL)	N = 2480 0.2	N = 2475 0.1
Uric acid (mg/dL)	N = 2318 0.2	N = 2333 0.0
Potassium* (mEq/L)	N = 2307 0.1	N = 2295 -0.1
BUN (mg/dL)	N = 2480 5.9	N = 2475 3.3

*excluding values ≥ 7 mEq/L

N = number of patients who had a baseline value and at least one post-baseline value

In all 3 datasets, patients in the valsartan groups had higher percentages of patients with creatinine, uric acid, potassium, and BUN exceeding specified limits than those in the active control and/or placebo groups. No other clinically meaningful percent changes from baseline

were observed. Results for the primary dataset at final visit (all biochemistry parameters) and at any timepoint (creatinine, uric acid, potassium and BUN only) are shown in Tables 4-23 and 4-24, respectively. Results for Study 107 (creatinine, uric acid, potassium and BUN only) at endpoint are shown in Table 4-25.

Table 4-23. Number (%) of patients with specified percent change from baseline to final visit for selected biochemistry variables (primary dataset)

Parameter Limit %	Valsartan n (%)	Active control ¹ n (%)	Placebo n (%)
Creatinine			
≥ 50% increase	123 (3.9)	1 (1.2)	24 (0.9)
Uric acid			
≥ 50% increase	93 (3.2)	2 (2.8)	48 (1.9)
Potassium*			
≥ 20% decrease	81 (2.7)	0	104 (4.2)
≥ 20% increase	298 (10.0)	5 (6.0)	128 (5.1)
BUN			
≥ 50% increase	506 (16.6)	4 (5.0)	168 (6.3)
SGPT (ALT)			
≥ 150% increase	33 (1.3)	2 (2.6)	26 (1.3)
SGOT (AST)			
≥ 150% increase	11 (0.4)	0	10 (0.5)
Alkaline phosphatase			
≥ 100% increase	17 (0.6)	1 (6.7)	14 (0.6)
Total bilirubin			
≥ 100% increase	74 (2.6)	1 (6.7)	77 (3.1)
Glucose			
≥ 50% decrease	44 (1.9)	0	38 (1.6)
≥ 50% increase	108 (4.6)	1 (6.7)	110 (4.8)
Sodium			
≥ 5% decrease	53 (1.7)	1 (1.2)	42 (1.6)
≥ 7% increase	12 (0.4)	1 (1.2)	14 (0.5)
Calcium			
≥ 10% decrease	59 (2.1)	3 (20.0)	45 (1.8)
≥ 10% increase	78 (2.7)	3 (20.0)	57 (2.3)

The primary dataset consisted of Studies 103, 104, 106, 107 (first 4 months) and 110

¹Combines lisinopril and enalapril treatment groups

*excluding values ≥ 7.0 mEq/L

Table 4-24. Number (%) of patients with specified percent change from baseline at any timepoint for selected biochemistry variables (primary dataset)

Parameter	Valsartan n (%)	Active control ¹ n (%)	Placebo n (%)
Creatinine			
≥ 50% increase	N = 3178 213 (6.7)	N = 84 2 (2.4)	N = 2699 47 (1.7)
Uric acid			
≥ 50% increase	N = 2937 107 (3.6)	N = 71 3 (4.2)	N = 2506 49 (2.0)
Potassium*			
≥ 20% increase	N = 2989 693 (23.2)	N = 84 7 (8.3)	N = 2509 343 (13.7)
BUN			
≥ 50% increase	N = 3047 888 (29.1)	N = 80 8 (10.0)	N = 2666 307 (11.5)

The primary dataset consisted of Studies 103, 104, 106, 107 (first 4 months) and 110

¹Combines lisinopril and enalapril treatment groups

*excluding values ≥ 7.0 mEq/L

N = number of patients who had a baseline value and at least one post-baseline value

Source: Post-text table 6.1-12

Table 4-25. Number (%) of patients with specified percent change from baseline to final visit for selected biochemistry variables (Study 107)

Parameter	Valsartan n (%)	Placebo n (%)
Creatinine		
≥ 50% increase	N = 2480 163 (6.6)	N = 2475 87 (3.5)
Uric acid		
≥ 50% increase	N = 2318 112 (4.8)	N = 2333 96 (4.1)
Potassium*		
≥ 20% increase	N = 2307 262 (11.4)	N = 2295 160 (7.0)
BUN		
≥ 50% increase	N = 2480 609 (24.6)	N = 2475 389 (15.7)

*excluding values ≥ 7.0 mEq/L

N = number of patients who had a baseline value and at least one post-baseline value

Dose-related effects: biochemistry parameters

In Study 106, possible dose-related effects were observed in the laboratory analyses for BUN, as shown in Table 4-26. There were no dose-related effects on serum creatinine.

Table 4-26. Number (%) of patients with BUN values exceeding 50% change from baseline limit at endpoint (Study 106; safety analyzable patients)

	Limit	Placebo n (%)	Valsartan 40 mg BID n (%)	Valsartan 80 mg BID n (%)	Valsartan 160 mg BID n (%)
BUN	+50%	N = 172 16 (9.3)	N = 168 17 (10)	N = 174 27 (16)	N = 171 34 (20)

N = number of patients who had a baseline value and at least one post-baseline value

Hematology

In all 3 datasets, mean and median values for all hematology variables and changes from baseline were clinically unremarkable in all treatment groups. Mean changes from baseline to final visit are presented for all hematology parameters for the primary dataset in Table 4-27 and for hemoglobin and hematocrit for long-term Study 107 in Table 4-28.

Table 4-27. Mean changes from baseline to final hematology parameter results (primary dataset)

Parameter	Valsartan	Active control ¹	Placebo
Hemoglobin (g/dL)	-0.4	-0.1	0.0
Hematocrit (%)	-1.3	-0.4	0.0
RBC (10 ¹² /L)	-0.2	-0.1	0.0
WBC (10 ⁹ /L)	0.0	0.2	0.0
Platelet count (10 ⁹ /L)	3.2	3.3	1.8

The primary dataset consisted of Studies 103, 104, 106, 107 (first 4 months) and 110

¹Combines lisinopril and enalapril treatment groups

Table 4-28. Mean changes from baseline to final hemoglobin and hematocrit results (Study 107)

	Valsartan	Placebo
Hemoglobin (g/dL)	N = 2313 -0.3	N = 2328 0.0
Hematocrit (%)	N = 2313 -1.1	N = 2328 -0.1

N = number of patients who had a baseline value and at least one post-baseline value

No clinically relevant differences between treatment groups were observed in the incidence of patients exceeding specified limits for white blood cell count or neutrophil count in any

dataset. In the primary dataset, and in Study 107, valsartan-treated patients had slightly higher percentages of patients who exhibited decreases of $\geq 20\%$ in hemoglobin and hematocrit compared to those in the placebo and/or active treatment groups. The small number of patients in the lisinopril group of dataset B (N = 13-15) prevent meaningful comparisons to valsartan and placebo. Results for the primary dataset (hemoglobin, hematocrit, WBC and absolute neutrophils) and Study 107 (hemoglobin and hematocrit, $\geq 20\%$ decrease only) are shown in Tables 4-29 and 4-30, respectively.

Table 4-29. Number (%) of patients with hematology values exceeding specified % change from baseline limit to final test result (primary dataset)

Parameter Limit %	Valsartan n (%)	Active control ¹ n (%)	Placebo n (%)
Hemoglobin			
$\geq 20\%$ decrease	56 (1.9)	1 (1.3)	20 (0.8)
$\geq 50\%$ increase	3 (0.1)	0	2 (0.1)
Hematocrit			
$\geq 20\%$ decrease	67 (2.3)	1 (1.3)	21 (0.9)
$\geq 50\%$ increase	10 (0.4)	0	9 (0.4)
WBC (leukocytes)			
$\geq 50\%$ decrease	12 (0.4)	0	5 (0.2)
$\geq 50\%$ increase	78 (2.7)	3 (3.8)	53 (2.2)
Absolute neutrophils			
$\geq 50\%$ decrease	49 (1.7)	0	30 (1.2)
$\geq 50\%$ increase	177 (6.3)	0	156 (6.4)

The primary dataset consisted of Studies 103, 104, 106, 107 (first 4 months) and 110

¹Combines lisinopril and enalapril treatment groups

N = number of patients who had a baseline value and at least one post-baseline value

Table 4-30. Number (%) of patients with hemoglobin and hematocrit values exceeding specified % change from baseline limit to final test result (Study 107)

Parameter	Limit	Valsartan N = 2313 n (%)	Placebo N = 2328 n (%)
Hemoglobin	-20%	70 (3.0)	44 (1.9)
Hematocrit	-20%	85 (3.7)	57 (2.5)

N = number of patients who had a baseline value and at least one post-baseline value

The patients included in these studies, in addition to taking valsartan, have been optimally treated with other heart failure medications including ACE inhibitors, beta-blockers, diuretics, digoxin and other medications which act on the RAS (ie spironolactone). In light of this combined therapy, it is not unexpected that these patients experience effects that are directly

related to inhibiting the RAS, such as signs and symptoms of hypotension (dizziness, syncope, orthostatic changes) and effects on the renal system (increased BUN, potassium and creatinine). In general, these effects are not exclusive to valsartan, but may be expected with multiple drug therapies used to treat heart failure.

The incidence of elevated BUN, creatinine and potassium with valsartan is consistent with the AE data, which showed higher rates of renal impairment and hyperkalemia with valsartan compared to placebo.

4.5. Other safety assessments

Summary statistics for sitting/standing systolic and diastolic blood pressure in Study 107 are summarized at selected timepoints in Table 4-31.

Table 4-31. Mean change from baseline in sitting/standing systolic and diastolic blood pressure at select timepoints (Study 107)

Blood pressure (mmHg)	Time	n	Valsartan N=2506		n	Placebo N=2494	
			Baseline mean	Mean change (SD)		Baseline mean	Mean change (SD)
Sitting – systolic	6 Months	2203	123.8	-5.8 (15.9)	2261	124.5	-1.9 (15.4)
	1 Year	2018	123.9	-5.2 (16.0)	2093	124.9	-1.3 (15.9)
	2 Years	1209	124.0	-5.6 (17.1)	1248	124.6	-2.4 (17.5)
	3 Years	123	123.9	-3.4 (17.6)	130	124.1	-0.8 (18.5)
	Endpoint	2494	123.4	-7.1 (17.8)	2482	120.4	-3.7 (17.5)
Sitting – diastolic	6 Months	2201	75.8	-4.0 (10.0)	2261	75.8	-1.4 (10.0)
	1 Year	2017	75.8	-3.8 (10.1)	2093	76.1	-1.2 (10.1)
	2 Years	1209	76.2	-4.5 (10.7)	1247	76.3	-2.5 (10.7)
	3 Years	122	74.9	-5.0 (10.1)	130	75.1	-3.3 (10.1)
	Endpoint	2494	75.5	-4.7 (11.0)	2482	75.6	-3.0 (10.8)

SD = Standard deviation

The reductions in sitting and standing systolic and diastolic blood pressure were greater in valsartan-treated patients than in placebo-treated patients at all assessments throughout the study. These reductions were apparent within the initial 2 weeks of therapy with valsartan and were sustained during the remainder of the active treatment period.

Blood pressure measurements were also collected to evaluate postural hypotension. The numbers and percentages of valsartan, active control (ie lisinopril and enalapril) and placebo-treated patients with decreases from sitting to standing blood pressures exceeding ≥ 10 mm Hg and/or ≥ 20 mm Hg are presented in Table 4-32 for the primary dataset and Study 107. No clinically relevant differences between or across treatment groups were observed in either dataset. Within each dataset, the results were comparable for valsartan and placebo. Although the proportions of patients with specified decreases were higher in Study 107 than in the primary dataset, this is due to the fact that patients in Study 107 had more assessments

(18 visits over the course of 3 years) than patients in the primary dataset. These results do not suggest a higher incidence of postural hypotension with valsartan compared to placebo. This appears to be inconsistent with spontaneous reporting of postural hypotension as adverse events, for which the investigators were able to determine postural hypotension without a specific definition. (In the primary dataset, the incidence of postural hypotension was 2.1% for valsartan and 0.7% for placebo. In long-term Study 107, the incidence of postural hypotension was 3.8% for valsartan and 1.9% for placebo.)

Table 4-32. Number (%) of patients exceeding specified decreases from sitting to standing blood pressure values at any post-baseline timepoint, by dataset

	Valsartan n (%)	Active control n (%)	Placebo n (%)
Double-blind controlled short-term trials 103, 104, 106, 110 and 107 (through visit 7)			
	N = 3720	N = 84	N = 2728
Decrease from sitting to standing diastolic BP \geq 10 mm Hg at any post-baseline timepoint	630 (19.3)	17 (20.2)	544 (19.9)
Decrease from sitting to standing systolic BP \geq 20 mmHg at any post-baseline visit	335 (10.2)	12 (14.3)	283 (10.4)
Decrease from sitting to standing diastolic BP \geq 10 mmHg at any post-baseline timepoint and/or decrease from sitting to standing systolic BP \geq 20 mmHg at any post-baseline timepoint	815 (24.9)	25 (29.8)	701 (25.7)
Double-blind placebo-controlled long-term trial 107			
	N = 2492	--	N = 2482
Decrease from sitting to standing diastolic BP \geq 10 mm Hg at any post-baseline timepoint	851 (34.1)	--	864 (34.8)
Decrease from sitting to standing systolic BP \geq 20 mmHg at any post-baseline visit	461 (18.5)	--	484 (19.5)
Decrease from sitting to standing diastolic BP \geq 10 mmHg at any post-baseline timepoint and/or decrease from sitting to standing systolic BP \geq 20 mmHg at any post-baseline timepoint	1035 (41.5)	--	1057 (42.6)
N = number of patients with both sitting and standing measurements for at least one post-baseline timepoint.			

4.6. Safety summary and conclusions

Adverse events

In the primary dataset (all controlled short-term trials), the overall incidence of adverse events for the valsartan and placebo group were 72.5% and 68.5%, respectively. Results for the dataset of placebo-controlled trials were similar to the primary dataset. As expected, more patients experienced an adverse event regardless of relationship to study drug with long term

administration (Study 107). The difference in incidence of adverse events between the valsartan (91.6%) and placebo (89.6%) treatment groups was small.

In all 3 datasets, the most frequently reported adverse events were dizziness excluding vertigo and hypotension NOS. Dizziness and hypotension were also the most frequently reported events suspected to be related to study medication in all 3 datasets. The incidence of these events was greater in patients treated with valsartan compared to placebo. This is consistent with the nature of treatment, the known effects of angiotensin II receptor blockers, and not unexpected in this patient population already receiving background therapy that could include ACE inhibitors, beta blockers, digoxin and diuretics.

The incidence of cough was similar for valsartan and placebo (4.9% for valsartan and placebo in the primary dataset and in dataset B; 10.3% for valsartan and 10.7% for placebo in long-term Study 107).

Adverse events in demographic subgroups

In the primary dataset and the long-term dataset (Study 107), the overall incidence of adverse events was generally unrelated to the race, gender, or age of the patients. In the long-term dataset (Study 107), the overall incidence of adverse events was generally unrelated to background use of ACE inhibitors or beta blockers at baseline.

Relation to dose and duration of therapy

Because of the forced-titration study design of Study 107, and different durations of therapy for each dose level, relation to dose could not be assessed in any ISS dataset. In Study 106, a parallel design trial, no dose response relationship was observed for any adverse event with the possible exception of hyperkalemia.

In the primary dataset, for events that occurred in $\geq 2\%$ of the valsartan-treated patients, the times to onset in the valsartan group were generally comparable to the placebo group. In long-term Study 107, the times to onset of most adverse events in the valsartan and placebo groups were comparable with the exception of dizziness excluding vertigo, hypotension NOS and renal impairment NOS which occurred earlier with valsartan compared to placebo.

Deaths

A total of 19 deaths occurred during the double-blind controlled short-term trials 103, 104, 106 and 110 (valsartan 10 patients, 1.3%; placebo 4 patients, 1.6%). The small number of deaths in this dataset prevents meaningful comparison between treatment groups regarding individual causes of death. The most frequently reported cause of death in all treatment groups was unexplained sudden death (valsartan 0.3%; placebo 0.8%). Otherwise, most of the deaths were of cardiac causes. None of the deaths that occurred in valsartan-treated patients were suspected to be related to study drug.

There were no major differences between treatments in the overall incidence rates (valsartan 20.1%; placebo 20.0%) or individual causes of death in long-term Study 107. They were predominantly cardiovascular related, and not unexpected in this patient population. The

most common cause of death in both groups was sudden death - unexpected, instantaneous or during sleep (valsartan 7.7%; placebo 7.1%).

Serious adverse events

No clinically relevant differences were observed between treatment groups for the overall (valsartan 16.7%; placebo 17.9%) or individual SAE rates in the primary dataset. The most frequently reported SAE in the primary dataset was congestive cardiac failure (valsartan 2.0%; placebo 2.9%). None of the SAEs were unexpected in the study population.

Similarly, for Study 107 no clinically relevant differences were observed between treatment groups for the overall (valsartan 51.2%; placebo 53.8%) or individual SAE rates. The most frequently reported individual SAE in Study 107 was sudden death unexplained (valsartan 5.4%; placebo 6.1%) followed by chest pain (4.8% for both groups).

Relatively few SAEs were suspected to be related to study medication [(primary dataset: valsartan 3.1%; placebo 1.9%) (Study 107: valsartan 7.7%; placebo 5.4%)]. The SAEs most frequently suspected to be related to study medication were hypotension and renal impairment.

Discontinuations due to adverse events

In double-blind controlled short-term trials 103, 104, 106 and 110, 8.6% of valsartan-treated patients and 3.7% of placebo-treated patients were discontinued due to adverse events. In this dataset, the most frequently reported events leading to discontinuation were hypotension NOS (valsartan 2.4%; placebo 0%) and dizziness excluding vertigo (valsartan 2.2%; placebo 0%).

In long-term Study 107, 9.9% of valsartan-treated patients and 7.3% of placebo-treated patients were discontinued due to adverse events. In this study, the most frequently reported events leading to discontinuation were dizziness excluding vertigo (valsartan 1.6%; placebo 0.4%), hypotension NOS (valsartan 1.3%; placebo 0.8%) and renal impairment NOS (valsartan 1.1%; placebo 0.2%).

Laboratory evaluations

Representative laboratory tests of hematopoietic, hepatic and renal function were performed at baseline and during treatment in the HF program for valsartan. Laboratory data for 6120 patients in the primary dataset, of whom 3289 received valsartan, were pooled across protocols in order to assess changes or trends that were not observed in individual clinical trials.

Laboratory data was evaluated for changes in group means and for trends of summary counts of individual patients who met limits for percent changes in laboratory data.

Biochemistry

Except for BUN, mean and median changes for all biochemistry variables were clinically unremarkable in all treatment groups in the primary dataset, dataset B, and Study 107. The valsartan group had slightly higher mean and median increases in BUN than the active control group and/or the placebo group in all 3 datasets. Otherwise, mean and median values for all

biochemistry variables and changes from baseline were clinically unremarkable and no clinically relevant differences between treatment groups were observed.

In all 3 datasets, patients in the valsartan groups had higher percentages of patients with creatinine, uric acid, potassium, and BUN exceeding specified limits than those in the active control and/or placebo groups at endpoint, and at any post-baseline visit.

In Study 106, possible dose-related effects were observed in the laboratory analyses for BUN. There were no dose-related effects on serum creatinine. Most patients in Study 106 (and in the entire integrated safety population) were receiving diuretics and ACE inhibitors as part of their background therapy for heart failure in addition to valsartan. Some patients were receiving spironolactone. These agents are known to increase the risk of elevations in BUN in some circumstances, particularly in heart failure patients.

The BUN and creatinine results were not unexpected. As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals, such as severe heart failure patients, whose renal function may depend on the activity of the renin-angiotensin-aldosterone system.

Approximately 89 - 93% of the patients in the primary dataset, dataset B and Study 107 were taking concomitant ACE inhibitors. The potassium results suggest that aldosterone suppression was augmented by the combination of an ACE inhibitor and an angiotensin receptor blocker.

Hematology

In all 3 datasets, mean and median values for all hematology variables and changes from baseline were clinically unremarkable in all treatment groups.

The analyses of patients exceeding specified percent changes from baseline show that in the primary dataset, and in Study 107, valsartan-treated patients had slightly higher percentages of patients who exhibited decreases of $\geq 20\%$ in hemoglobin and hematocrit compared to those in the placebo and/or active treatment groups. This was also found in the analysis comparing baseline to any post-baseline result.

The clinical significance of the hemoglobin and hematocrit results is unclear, but consistent with previous experience with angiotensin receptor blockers and ACE inhibitors.

Summary of laboratory data

From these data it can be concluded that valsartan:

Was associated with increases from baseline to endpoint in serum creatinine, BUN, uric acid, and potassium more frequently than patients treated with placebo. For valsartan treated patients, 3.9% had a $\geq 50\%$ increase in serum creatinine compared to 0.9% of placebo-treated patients; 16.6% had a $\geq 50\%$ increase in BUN compared to 6.3% of placebo-treated patients; 3.2% had a $\geq 50\%$ increase in uric acid compared to 1.9% of placebo-treated patients, and 10.0% had a $\geq 20\%$ increase in serum potassium compared to 5.1% of placebo-treated patients in the primary dataset;

May be associated with decreases in hemoglobin and hematocrit. In the primary dataset, 1.9% of valsartan patients had a $\geq 20\%$ decrease in hemoglobin and 2.3% had a $\geq 20\%$ decrease in hematocrit. These rates were higher than those observed in the placebo group (0.8% and 0.9%, respectively);

Was not associated with neutropenia in this population.

No special monitoring of laboratory parameters is necessary per se with valsartan, but the evaluation and monitoring of patients with HF, especially those receiving concomitant therapy with diuretics and other inhibitors of the RAS, should always include assessment of renal function.

5. Overall Benefit/Risk Assessment

The data obtained in this clinical program are sufficient upon which to base a critical assessment of the safety and tolerability of valsartan in the population of patients with Class II-IV heart failure.

Valsartan significantly reduced the risk by 13.2% ($p = 0.009$) for time to first morbid event, defined as all-cause mortality, heart failure hospitalization, sudden death with resuscitation, and need for intravenous vasodilator or inotropic therapy, compared to placebo in patients with NYHA Class II-IV heart failure. All cause mortality was similar in the valsartan and placebo treated patients. The primary benefit was a 27.5% ($p = 0.00001$) reduction in risk for time to first heart failure hospitalization. The benefits were greatest in patients not receiving either an ACE inhibitor or a beta-blocker. However, risk ratios favoring placebo were observed in those treated with both a beta-blocker and an ACE inhibitor. Subgroup analyses can be difficult to interpret and it is not known whether these represent true differences or chance effects.

Valsartan also demonstrated statistically significant beneficial effects on NYHA Class, signs and symptoms, quality of life, left ventricular volume and ejection fraction, and norepinephrine and brain natriuretic peptide compared to placebo. In shorter term studies (12-16 weeks), improvement in exercise capacity was demonstrated and valsartan was shown to be comparable to enalapril in improvement in exercise capacity, but statistically significant differences from placebo were not demonstrated. Beneficial hemodynamic effects were observed in smaller trials of 4 weeks duration.

These improvements in outcomes, signs and symptoms, quality of life, and several surrogate markers of efficacy are accompanied by a small risk of dizziness and hypotension as well as renal dysfunction. There were few unexpected adverse events observed in this clinical program. No special monitoring of laboratory parameters is necessary per se with valsartan, but the evaluation and monitoring of patients with HF, especially those receiving concomitant therapy with diuretics and other inhibitors of the RAAS, should always include assessment of renal function. These findings confirm that the benefit/risk profile for valsartan is very favorable.

6. Reference List

1. Massie BM and Shah NB. Evolving trends in the epidemiologic factors of heart failure: Rationale for preventive strategies and comprehensive disease management. *Am Heart J* 1997; 133: 703-712.
2. Heart Failure Society of American (HFSA) practice guidelines. HFSA guidelines for management of patients with heart failure caused by left ventricular systolic dysfunction-pharmacological approaches. *J Card Fail* 1999; 5: 357-382.
3. Consensus recommendations for the management of chronic heart failure. On behalf of the membership of the advisory council to improve outcomes nationwide in heart failure. *AM J Cardiol* 1999; 83 (2A): 1A-38A.
4. ACC/AHA Task Force Heart Failure Guidelines. Guidelines for the evaluation and management of heart failure. Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Evaluation and Management of Heart Failure). *JACC* 1995; 26: 1376-1398.
5. Konstam MA, Dracup K, Baker D, et al. Heart failure: evaluation and care of patients with left ventricular systolic dysfunction. Rockville, MD. Agency for Health Care Policy and Research. US Dept. of Health and Human Services. 1994.
6. The treatment of heart failure. Task Force of the Working Group on Heart Failure of the European Society of Cardiology. *Eur Heart J* 1997; 18: 736-753.
7. Urata H, Healy B, Stewart RW, et al. Angiotensin II-forming pathways in normal and failing hearts. *Circ Res*. 1990; 66:883-890
8. Urata H, Kinoshita A, Misono KS, et al. Identification of a highly specific chymase as the major angiotensin II-forming enzyme in the human heart. *J Biol Chem* 1990; 265: 22348-22357.
9. Rousseau MF, Konstam MA, Benedict CR et al, Progression of Left Ventricular Dysfunction Secondary to Coronary Artery Disease, Sustained Neurohormonal Activation and Effects of Ibopamine Therapy During Long-Term Therapy with Angiotensin-Converting Enzyme Inhibitor. *Am J Card* 1994; 73: 488-493.
10. Gavras I. Bradykinin-mediated effects of ACE inhibition. *Kidney Int* 1992; 42: 1020-1029.
11. Pfeffer MA. Enhancing cardiac protection after myocardial infarction: rational for newer clinical trials of angiotensin receptor blockers. *Am Heart J* 2000; 139 (1 Pt2): S23-28.

7. Tables of Studies

Company Finished Product Active Substance		PHARMACODYNAMIC STUDIES IN PATIENTS			General Results & Adverse Events % AEs % SAEs																																						
Protocol No. & Study Dates Investigator & Country Publication Reference		Study Design & Purpose Population Studied Evaluations	Total No. & Race (w,b,o) Age Range (mean) Group No. & Sex (m,f)	Treatment & Route Duration of Therapy Dose & Regimen																																							
7.1. Pharmacodynamic studies in patients																																											
<p>protocol: 102</p> <p>invest.: Dr P Carson, Dr TB Levine, Dr S Gottlieb</p> <p>country: USA</p> <p>start: 12-Mar-1993</p> <p>end: 4-Apr-1994</p> <p>publ.: Carson PE, et al.</p> <p>Pharmacokinetics, Neurohormone levels and Safety Evaluation of Single doses of Valsartan in Patients with Congestive Heart Failure.</p> <p>J Cardiac Failure: 5, 3 (suppl 1): 62, 1999. (presented at the HFSA 1999)</p> <p>Feliciano N, et al. Acute hemodynamic effects of single oral doses of valsartan in patients with heart failure. Abstract presented at "Heart Failure-1995" Meeting, Amsterdam, 1995.</p>		<p>Design, goal & population:</p> <p>Open-label, multicenter, randomized, parallel group, placebo controlled, dose ranging trial to determine the acute central hemodynamic effects of valsartan in patients with stable chronic congestive heart failure.</p> <p>Patients included were between 18-80 y, NYHA Class III-IV, LVEF≤35% and had stable chronic CHF for > 4 weeks prior to visit 1.</p> <p>Evaluations:</p> <p>Efficacy measures included: change from baseline for PCWP, CO, RAP, CI, SVR, SVI, PVR, DPAP, SPAP, MPAP, HR, SBP, DBP, MAP; and plasma AII, PRA, and ALDO levels.</p>	<p>total: 25 (6 w,19 b,0 o)</p> <p>age: 50.9 (27-71)</p> <p>groups:</p> <table><tr><td>4</td><td>(4 m, 0 f)</td></tr><tr><td>5</td><td>(3 m, 2 f)</td></tr><tr><td>4</td><td>(4 m, 0 f)</td></tr><tr><td>3</td><td>(2 m, 1 f)</td></tr><tr><td>4</td><td>(4 m, 0 f)</td></tr><tr><td>5</td><td>(5 m, 0 f)</td></tr></table>	4	(4 m, 0 f)	5	(3 m, 2 f)	4	(4 m, 0 f)	3	(2 m, 1 f)	4	(4 m, 0 f)	5	(5 m, 0 f)	<p>form: capsule 10mg, 20 mg, 40 mg, 80 mg, 160 mg and placebo</p> <p>duration: 1 dose</p> <p>doses:</p> <table><tr><td>Placebo</td><td>po 1 dose</td></tr><tr><td>Valsartan 10 mg</td><td>po 1 dose</td></tr><tr><td>Valsartan 20 mg</td><td>po 1 dose</td></tr><tr><td>Valsartan 40 mg</td><td>po 1 dose</td></tr><tr><td>Valsartan 80 mg</td><td>po 1 dose</td></tr><tr><td>Valsartan 160 mg</td><td>po 1 dose</td></tr></table>	Placebo	po 1 dose	Valsartan 10 mg	po 1 dose	Valsartan 20 mg	po 1 dose	Valsartan 40 mg	po 1 dose	Valsartan 80 mg	po 1 dose	Valsartan 160 mg	po 1 dose	<p>Single doses of 10 mg, 20 mg, 40 mg, 80 mg and 160 mg valsartan were safe and tolerable in patients with chronic stable heart failure. Clinically important improvements in PCWP and CO could not be defined in this trial due to the small sample size.</p> <table><tr><td>AE%</td><td>SAE%</td></tr><tr><td>50.0</td><td>0</td></tr><tr><td>40.0</td><td>0</td></tr><tr><td>25.0</td><td>0</td></tr><tr><td>66.7</td><td>0</td></tr><tr><td>0</td><td>0</td></tr><tr><td>60.0</td><td>20.0</td></tr></table> <p>Total AE's for valsartan group = 38.1% None of the AEs or the SAE were considered related to study drug.</p>	AE%	SAE%	50.0	0	40.0	0	25.0	0	66.7	0	0	0	60.0	20.0
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Company Finished Product Active Substance		PHARMACOKINETIC STUDIES IN PATIENTS				
Protocol No. & Study Dates Investigator & Country Publication Reference		Study Design & Purpose Population Studied Evaluations	Total No. & Race (w,b,o) Age Range (mean) Group No. & Sex (m,f)	Treatment, Route, Regimen Duration of Therapy Dosage	General Results & Adverse Events % AEs % SAEs	
7.2. Pharmacokinetic studies in patients						
<p>protocol: 105</p> <p>invest.: Dr Jon Ruckel</p> <p>countries: USA</p> <p>start: 2-Aug 1997</p> <p>end: 6-Nov-1997</p> <p>publ.: Prasad P, et al. The pharmacokinetics of multiple doses of valsartan in congestive heart failure patients. Clin Pharmacol Ther 2000;67:118</p> <p>Prasad, et al. The effects of age on the pharmacokinetics of valsartan in congestive heart failure patients. Clin Pharmacol Ther 2000;67:118</p>		<p>Design, goal & population:</p> <p>Open label, two phase, four period and multiple dose study to assess the pharmacokinetics of valsartan in patients with congestive heart failure</p> <p>Patients included were between 18-75 y, NYHA Class II-III, LVEF ≤ 40% and had stable CHF for >1 month prior to visit 1</p> <p>Evaluations:</p> <p>Pharmacokinetic parameters evaluated were Cmax, T max, AUC, T½, dosing interval, clearance adjusted to body weight, accumulation factor and fluctuation index.</p> <p>Tolerability measures included blood pressure, pulse, body weight and laboratory safety tests.</p>	<p>total: 20</p> <p>18 completed (15 w,3 b)</p> <p>age: 63.1 (43-79)</p>	<p>form: capsule, valsartan 40 mg, 80 mg and 160 mg</p> <p>duration: 22 days</p>	<p>Pharmacokinetics (AUC and Cmax) of valsartan showed a linear and almost dose proportional relationship in dose range 40mg-160 mg bid. The clearance of valsartan appeared to be lessened in CHF patients as compared to healthy patients. There appeared to be a slight accumulation of valsartan in the bid regimen in CHF patients. Valsartan was well tolerated in doses up to 160 mg bid by patients with CHF.</p>	
			<p>groups:</p> <p>7</p> <p>7</p> <p>6</p> <p>20</p> <p>19</p> <p>18</p>	<p>doses:</p> <p>Day 1: Valsartan 40 mg po x1 dose</p> <p>Day 1: Valsartan 80 mg po x 1 dose</p> <p>Day 1: Valsartan 160 mg po x 1 dose</p> <p>Day 2-8: Valsartan 40 mg po bid</p> <p>Day 9-15: Valsartan 80 mg po bid</p> <p>Day 16-22: Valsartan 160 mg po bid</p>	<p>AE% SAE%</p> <p>42.9 0</p> <p>42.9 0</p> <p>66.7 0</p> <p>65.0 5.0</p> <p>52.6 0</p>	

Company Finished Product Active Substance		PLACEBO CONTROLLED STUDIES IN PATIENTS			General Results & Adverse Events % AEs % SAEs	
Protocol No. & Study Dates Investigator & Country Publication Reference		Study Design & Purpose Population Studied Evaluations	Total No. & Race (w,b,o) Age Range (mean) Group No. & Sex (m,f)	Treatment, Route, Regimen Duration of Therapy Dosage		
7.3. Placebo controlled studies in patients						
<p>protocol: 103</p> <p>invest.: Prof. Dr. V. Mazayev, Dr Sulimov, Dr T. Zwereva, Prof. Dr L. Olbinskaya, Prof. Dr L. Fomina, Prof. Dr V.A. Lyusov. Prof. Dr V.A. Orlov</p> <p>country: Russia</p> <p>start: 14-Apr-1995</p> <p>end: 28-Mar-1996</p> <p>publ.: Mazayev VP, et al. Valsartan in heart failure patients previously untreated with an ACE inhibitor. In J Cardiol 1998 Aug;65(3):239-46.</p>		<p>Design, goal & population: Multicenter, randomized, double blind, placebo- and active-controlled trial to assess the cardiac hemodynamic effects of valsartan 40mg, 80 mg and 160 mg , all given bid, in patients with chronic stable CHF treated for four weeks. Patients included were between 18-80 y, NYHA Class II-IV, PCWP≥ 15 mmHg and had not taken an ACEI for at least 6 months prior to entry.</p> <p>evaluations: Efficacy measures included: change in baseline for PCWP, CO, RAP, CI, SVR, PVR, MAP, SPAP, DPAP, MPAP, SVI, HR, SBP, DBP, PRA; and plasma All, ALDO and NE levels.</p> <p>Tolerability measures include AE, routine lab tests, changes from baseline in HR, ambulatory blood pressure and body weight.</p>	<p>Total: 116 (all Caucasian) Completed: 103 age: 56 (24-80)</p> <p>groups:</p> <p>24 (18 m,6 f) 24 (23 m, 1 f) 27 (22 m, 5 f) 26 (23 m,3 f) 15 (10 m,5 f)</p>	<p>form: capsules, valsartan 40mg, 80 mg and 160 mg, placebo, lisinopril 5 mg and 10 mg</p> <p>duration: 4 weeks</p> <p>doses:</p> <p>Valsartan 40 mg po bid Valsartan 80 mg po bid Valsartan 160 mg po bid Placebo po bid Lisinopril 5 mg po qd x1week then 10 mg po qd x 3 weeks with matching placebo in the evening</p>	<p>Valsartan had beneficial effects on cardiac hemodynamics. These events were clinically relevant and statistically significant depending on the dose and timepoint. These effects were similar to those of an ACE inhibitor. No definite trends in laboratory abnormalities were observed, with the exception of slight increase in the number of patients experiencing increases in serum potassium and urea in the Valsartan and Lisinopril groups compared to placebo. Valsartan was generally well tolerated in this trial.</p> <p>AE% 45.8 37.5 55.6 30.8 60.0</p> <p>SAE% 8.3 8.3 3.7 0 0</p>	

Company Finished Product Active Substance	NOVARTIS Diovan® Valsartan	PLACEBO CONTROLLED STUDIES IN PATIENTS			General Results & Adverse Events % AEs % SAEs
		Protocol No. & Study Dates Investigator & Country Publication Reference	Study Design & Purpose Population Studied Evaluations	Total No. & Race (w,b,o) Age Range (mean) Group No. & Sex (m,f)	Treatment, Route, Regimen Duration of Therapy Dosage
		<p>protocol: 104</p> <p>invest.: Dr K. Adams, Dr I. Anand, Dr L. Baruch, Dr P. Carson, Dr F. Cobb, Dr I. Cohen, Dr R Davidson, Dr P. Deedwania, Dr W. Dunkman, Dr E. Eichhorn, Dr T. Heywood, Dr C. Hughes, Dr M. Icenogle, Dr C. Moore, Dr G. Pennoock, Dr R. Shabetai, Dr R Smith, Dr W. Stoever, Dr R. Taylor</p> <p>countries: USA</p> <p>start: 6-Mar-1995</p> <p>end: 8-Jun-1996</p> <p>publ.: Baruch L, et al.</p> <p>Augmented short and long term hemodynamic and hormonal effects of an angiotensin receptor blocker added to angiotensin converting enzyme inhibitor therapy in patients with heart failure. Circulation 1999 May 25;99(20):2658-64.</p>	<p>design, goal & population: Multicenter, randomized, parallel group, double-blind, placebo controlled, dose response trial to determine the acute and chronic central hemodynamic effects of valsartan in patients with symptomatic congestive heart failure.</p> <p>Patients included were ≥ 18y, NYHA Class II-IV, PCWP ≥ 15 mmHg and were on an ACEI for at least 4 weeks prior to visit 1.</p> <p>evaluations: Efficacy measures included: change in baseline for PCWP, CO, RAP, CI, SVR, PVR, SVI, MPAP, SPAP, DPAP, Map, HR, SBP, DBP; and Neurohormone levels (PRA, ALDO, NE, APEP, AII), Tolerability measures included SBP, DBP, HR, Routine lab tests</p>	<p>total: 83 (54 w, 22 b, 7 o) (74 completed)</p> <p>age: 64 (36-82)</p> <p>groups:</p> <p>28 28 27</p> <p>all patients were male</p>	<p>form: capsules, valsartan 80 mg and 160 mg, placebo, lisinopril 10 mg</p> <p>duration: 4 weeks</p> <p>doses:</p> <p>Placebo po bid Valsartan 80 mg bid Valsartan 160 mg bid</p> <p>AE% SAE%</p> <p>64.3 7.1 75.0 14.3 77.8 18.5</p> <p>Valsartan 80 and 160 mg bid had a beneficial effect on cardiac hemodynamics and neurohormones and was generally well tolerated by patients with stable CHF on ACEI therapy.</p>

Company Finished Product Active Substance	NOVARTIS Diovan® Valsartan	PLACEBO CONTROLLED STUDIES IN PATIENTS			Treatment, Route, Regimen Duration of Therapy Dosage	General Results & Adverse Events % AEs % SAEs
		Protocol No. & Study Dates Investigator & Country Publication Reference	Study Design & Purpose Population Studied Evaluations	Total No. & Race (w,b,o) Age Range (mean) Group No. & Sex (m,f)		
		<p>protocol: 106 invest.: Dr. I Anand, et al. countries: Argentina, Canada, USA, start: 18-August-1997 end: 23-May-2000 publ.: none</p>	<p>design, goal & population: Multicenter, randomized, double blind, placebo- controlled parallel trial to assess the effect of valsartan on exercise capacity, quality of life, and signs and symptoms in patients with stable chronic congestive heart failure. Patients included were ≥ 18y, NYHA Class II-IV and LVEF ≤40%.</p> <p>evaluations: Efficacy measures included: exercise tolerance, quality of life, signs and symptoms of CHF, LVEF, and NYHA Classification. Tolerability measures included routine laboratory, BP, HR, and body weight.</p>	<p>total: 770 (642w, 95 b, 33 o) age: 63.2 (26-91)</p> <p>groups: 192 (154m, 38f) 185 (146m, 39f) 195 (161m, 34f) 198 (158 m, 40f)</p>	<p>form: capsule, valsartan 40 mg, 80 mg and 160 mg, placebo duration: 4 months</p> <p>doses: Placebo po bid Valsartan 40 mg po bid Valsartan 80 mg po bid Valsartan 160 mg po bid</p>	<p>Valsartan in addition to standard CHF background therapy did not produce a statistically significant improvement in exercise tolerance or MLHFQ. A higher mean increase from baseline in ETT was observed in both valsartan and placebo groups. Positive trends were seen in two small subgroups: those not taking an ACEI and patients with CHF etiology of hypertension. Clinically and statistically significant improvements in LVEF were seen in the valsartan 40 mg and 160 mg bid treatment groups compared with placebo</p> <p>Non ETT AE% and SAE% 77.6 15.6 72.4 14.6 75.8 13.9 77.7 10.7</p> <p>The observed safety profile was consistent with the known pharmacological response to angiotensin receptor blocker and background heart failure therapies.</p>

Company Finished Product Active Substance	NOVARTIS Diovan® Valsartan	PLACEBO CONTROLLED STUDIES IN PATIENTS				
		Protocol No. & Study Dates Investigator & Country Publication Reference	Study Design & Purpose Population Studied Evaluations	Total No. & Race (w,b,o) Age Range (mean) Group No. & Sex (m,f)	Treatment, Route, Regimen Duration of Therapy Dosage	General Results & Adverse Events % AEs % SAEs
		<p>protocol: 107 invest.: Dr K Agarwal, Dr Janet Anderson, Dr Jerome Anderson, et al. countries: Australia, Belgium, Czech Republic, Denmark, Finland, France, Germany, Hungary, Italy, Norway, The Netherlands, South Africa, Spain, Sweden, United Kingdom, USA start: 16-Mar-1997 end: 5-Oct-2000 publ.: submitted</p>	<p>design, goal & population: Multicountry, randomized, double-blind, parallel, placebo-controlled trial to assess the effect of valsartan on morbidity and mortality, signs and symptoms and quality of life in patients with stable chronic CHF. Patients included were ≥ 18y, NYHA Class II-IV, LVEF ≤40% and LVIDD > 2.9 cm/m² and had stable chronic CHF for > 3 months prior to visit 1. evaluations: The primary efficacy variables included: time to death, time to first morbid event (death, sudden death with resuscitation, need for therapeutic doses of IV inotropes or vasodilators, hospitalization for CHF). Secondary variables included: time to first occurrence of morbid event other than death, time to cardiovascular related death, NYHA Class, change from baseline in LVEF, LVIDD, and QOL. Other variables included NE and BNP. Tolerability measures include blood pressure, pulse, weight, and routine laboratory tests.</p>	<p>total: 5010 (4526 w, 344 b, 140 o) age: 18-96 (62.7)</p> <p>groups: 2499 (2000 m, 499 f) 2511 (2007 m, 504 f)</p>	<p>form: capsule, valsartan 40mg, 80 mg and 160mg, placebo duration: up to 3 ½ years</p> <p>doses: Placebo 1 po bid All Valsartan (Valsartan 40 mg po bid Valsartan 80 mg po bid Valsartan 160 mg po bid) Forced titration</p>	<p>Valsartan in combination with existing therapies had a significantly favorable effect on morbidity (13.2% reduction), particularly CHF hospitalizations (27.5% reduction). Valsartan in combination with standard background therapies had a neutral effect on mortality. Valsartan demonstrated statistically significant beneficial effects on NYHA Class, signs/symptoms, LVEF, LVIDD, QOL, norepinephrine, and brain natriuretic peptide than placebo at endpoint.</p> <p>AE% SAE% 89.7 53.9 91.6 51.2</p> <p>Valsartan was safe and well tolerated in this study; deaths and serious adverse events were as expected in this patient population.</p>

Company Finished Product Active Substance		NOVARTIS Diovan® Valsartan		REFERENCE THERAPY CONTROLLED STUDIES IN PATIENTS		General Results & Adverse Events % AEs % SAEs	
Protocol No. & Study Dates Investigator & Country Publication Reference		Study Design & Purpose Population Studied Evaluations		Total No. & Race (w,b,o) Age Range (mean) Group No. & Sex (m,f)		Treatment, Route, Regimen Duration of Therapy Dosage	
7.4. Reference therapy controlled studies in patients							
protocol: 110 invest.: Dr R Willenheimer, Dr K Salden, Dr T Wallen, Dr k Schenck Gustafsson, Dr P Lofdahl, Dr U Dahlistrom, Dr E Pantav, Dr M Freitag, Dr C Sylven, Dr F Hustasaari, Dr M Edner, Dr B Friberg, countries: Sweden start: 16 August 1999 end: 25 April 2000 publ.: submitted		design, goal & population: Multicenter, randomized, active controlled study to assess the efficacy and safety of valsartan compared to enalapril on exercise capacity in patients with stable moderate chronic heart failure. Patients included were ≥ 18y, NYHA Class II-III, LVEF ≤45%, exercise capacity not limited by any disease other than CHF, ACEI therapy for > 3 months prior to visit 1.		total: 141 age: 67.7 (46-90) All patients were Caucasian.		form: capsule: valsartan 80mg and 160mg, placebo tablet: enalapril 5mg and 10 mg, placebo duration: 12 weeks doses: Valsartan 80 mg po qd x 1 week titrated to Valsartan 160 mg po qd Enalapril 5 mg po bid x1 week titrated to Enalapril 10 mg po bid	
		evaluations: Efficacy measures included: exercise capacity (six minute walk test), LVEF, dyspnea fatigue index, quality of life assessment. Tolerability measurements include blood pressure, pulse, weight, and safety laboratory tests.					
						Valsartan 80-160 mg given once daily was at least as effective, with respect to exercise capacity, and as well tolerated as enalapril 5-10 mg given twice daily in patients with CHF NYHA Class II-III previously treated with an ACEI. AE% SAE% 50.0 9.0 63.0 16.0	